

TITLE OF THE INVENTION
8-(BIARYL)QUINOLINE PDE4 INHIBITORS

BACKGROUND OF THE INVENTION

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FIELD OF THE INVENTION

The present invention is directed to compounds that are substituted 8-(biaryl)quinolines. In particular, this invention is directed to substituted 8-(biaryl)quinolines which are phosphodiesterase-4 inhibitors wherein the biaryl group 10 at the 8-position is in a *meta* relationship to the quinoline group.

RELATED BACKGROUND

Hormones are compounds that variously affect cellular activity. In many respects, hormones act as messengers to trigger specific cellular responses and 15 activities. Many effects produced by hormones, however, are not caused by the singular effect of just the hormone. Instead, the hormone first binds to a receptor, thereby triggering the release of a second compound that goes on to affect the cellular activity. In this scenario, the hormone is known as the first messenger while the second compound is called the second messenger. Cyclic adenosine monophosphate 20 (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as a second messenger for hormones including epinephrine, glucagon, calcitonin, corticotrophin, lipotropin, luteinizing hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin. Thus, cAMP mediates cellular 25 responses to hormones. Cyclic AMP also mediates cellular responses to various neurotransmitters.

Phosphodiesterases ("PDE") are a family of enzymes that metabolize 3', 5' cyclic nucleotides to 5' nucleoside monophosphates, thereby terminating cAMP 30 second messenger activity. A particular phosphodiesterase, phosphodiesterase-4 ("PDE4", also known as "PDE-IV"), which is a high affinity, cAMP specific, type IV PDE, has generated interest as potential targets for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist as at least four isoforms, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in allergic and/or inflammatory 35 responses. Thus, it is believed that inhibition of PDE4, particularly the specific PDE4 isoforms that produce detrimental responses, can beneficially affect allergy and

inflammation symptoms. It would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

A major concern with the use of PDE4 inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Burnouf et al., ("Burnouf"), *Ann. Rep. In Med. Chem.*, 33:91-109(1998). B.Hughes et al., *Br. J.Pharmacol.*, 118:1183-1191(1996); M.J.Perry et al., *Cell Biochem. Biophys.*, 29:113-132(1998); S.B.Christensen et al., *J.Med. Chem.*, 41:821-835(1998); and Burnouf describe the wide variation of the severity of the undesirable side effects exhibited by various compounds. As described in M.D.Houslay et al., *Adv. In Pharmacol.*, 44:225-342(1998) and D.Spina et al., *Adv. In Pharmacol.*, 44:33-89(1998), there is great interest and research of therapeutic PDE4 inhibitors.

International Patent Publication WO9422852 describes quinolines as PDE4 inhibitors. International Patent Publication WO9907704 describes 1-aryl-1,8-naphthylidin-4-one derivatives as PDE4 inhibitors.

A.H.Cook, et al., *J.Chem. Soc.*, 413-417(1943) describes gamma-pyridylquinolines. Other quinoline compounds are described in Kei Manabe et al., *J.Org. Chem.*, 58(24):6692-6700(1993); Kei Manabe et al., *J.Am. Chem. Soc.*, 115(12):5324-5325(1993); and Kei Manabe et al., *J.Am. Chem. Soc.*, 114(17):6940-6941(1992).

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 5,679,712, 5,693,672 and 5,747,541 describe substituted benzoylguanidine sodium channel blockers, U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

U.S. Patent Nos. 5,491,147, 5,608,070, 5,622,977, 5,739,144, 5,776,958, 5,780,477, 5,786,354, 5,798,373, 5,849,770, 5,859,034, 5,866,593, 5,891,896, and International Patent Publication WO 95/35283 describe PDE4 inhibitors that are tri-substituted aryl or heteroaryl phenyl derivatives. U.S. Patent No. 5,580,888 describes PDE4 inhibitors that are styryl derivatives. U.S. Patent No. 5,550,137 describes PDE4 inhibitors that are phenylaminocarbonyl derivatives. U.S. Patent No. 5,340,827 describes PDE4 inhibitors that are phenylcarboxamide compounds. U.S. Patent No. 5,780,478 describes PDE4 inhibitors that are tetra-substituted phenyl derivatives. International Patent Publication WO 96/00215

describes substituted oxime derivatives useful as PDE4 inhibitors. U.S. Patent No. 5,633,257 describes PDE4 inhibitors that are cyclo(alkyl and alkenyl)phenyl-alkenyl (aryl and heteroaryl) compounds.

However, there remains a need for novel compounds and compositions
5 that therapeutically inhibit PDE4 with minimal side effects.

SUMMARY OF THE INVENTION

The present invention is directed to novel substituted 8-(biaryl)quinolines that are PDE4 inhibitors, wherein the biaryl group at the 8-position
10 is in a *meta* relationship to the quinoline group. This invention also provides a pharmaceutical composition which includes an effective amount of the novel substituted 8-arylquinoline and a pharmaceutically acceptable carrier.

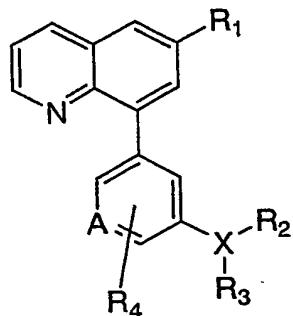
This invention further provides a method of treatment in mammals of,
for example, i) Pulmonary disorders such as asthma, chronic bronchitis, chronic
15 obstructive pulmonary disease (COPD), adult respiratory distress syndrome, infant respiratory distress syndrome, cough, chronic obstructive pulmonary disease in animals, adult respiratory distress syndrome, and infant respiratory distress syndrome, ii) Gastrointestinal disorders such as ulcerative colitis, Crohn's disease, and hypersecretion of gastric acid, iii) Infectious diseases such as bacterial, fungal or viral
20 induced sepsis or septic shock, endotoxic shock (and associated conditions such as laminitis and colic in horses), and septic shock, iv) Neurological disorders such as spinal cord trauma, head injury, neurogenic inflammation, pain, and reperfusion injury of the brain, v) Inflammatory disorders such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, inflammation and cytokine-mediated chronic
25 tissue degeneration, vi) Allergic disorders such as allergic rhinitis, allergic conjunctivitis, and eosinophilic granuloma, vii) Psychiatric disorders such as depression, memory impairment, and monopolar depression, viii) Neurodegenerative disorders such as Parkinson disease, Alzheimer's disease, acute and chronic multiple sclerosis, ix) Dermatological disorders such as psoriasis and other benign or
30 malignant proliferative skin diseases, atopic dermatitis, and urticaria, x) Oncological diseases such as cancer, tumor growth and cancerous invasion of normal tissues, xi) Metabolic disorders such as diabetes insipidus, xii) Bone disorders such as osteoporosis, and xiii) Cardiovascular disorders such as arterial restenosis, atherosclerosis, reperfusion injury of the myocardium, and xiv) Other disorders such
35 as chronic glomerulonephritis, vernal conjunctivitis, transplant rejection and graft

versus host disease, and cachexia – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cAMP levels – by the administration of an effective amount of the novel substituted 8-(biaryl)quinoline or a precursor compound which forms *in vivo* the novel substituted 5 8-(biaryl)quinoline.

In another aspect, the present invention is directed to a method of enhancing cognition in a healthy subject comprising administering a safe cognition enhancing amount of a phosphodiesterase-4 inhibitor. In particular, this invention is 10 directed to a method of enhancing memory, learning, retention, recall, awareness and judgement in health subjects comprising administering a safe and cognition enhancing amount of a phosphodiesterase-4 inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

15 A compound of this invention is represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

A is C or N;

20 X is phenyl, pyridyl, pyrazinyl, thiaphenyl, quinolinyl, benzofuranyl, oxadiazolyl, diazolypyridinyl, imidazolypyridinyl, oxadiazolylphenyl, or benzodioxolyl;

R1 is hydrogen, halogen; or -C1-6alkyl, -cycloC3-6alkyl, or -C1-6alkenyl group, wherein any of the groups is optionally substituted with 1-6 25 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO2-C1-6alkyl;

R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)2, -C₀₋₄alkyl(C₃₋₆cycloalkyl)2, -C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)2, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl(-C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)2, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)3, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;

optionally, R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and

any ring nitrogen optionally forms N-oxide or N-chloride.

30 In one aspect, the compound of this invention is represented by
Formula (I), or a pharmaceutically acceptable salt thereof, wherein.
A is C;

X is phenyl, pyridyl, pyrazinyl, thiaphenyl, quinolinyl, benzofuranyl, oxadiazolyl, diazolypyridinyl, imidazolypyridinyl, oxadiazolylphenyl, or benzodioxolyl;

R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or

- 5 -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁₋₆alkyl;

R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)2, -C₀₋₄alkyl(C₃₋₆cycloalkyl)2, -C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)2, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)2, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)3, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;

optionally, R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and

- 35 any ring nitrogen optionally forms N-oxide or N-chloride.

In an embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

- A is C;
- 5 X is phenyl;
- R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁₋₆alkyl;
- 10 R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-15 O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
- 35 35 optionally, R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and
any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In another embodiment of this one aspect, the compound of this
5 invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof,
wherein

- A is C;
X is thiaphenyl;
R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or
10 -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6
substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂₋
C₁₋₆alkyl;
- R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl.

6cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
optionally, R₂ forms =O with an adjoining bond;
5 R₄ is hydrogen, or halogen; and
any ring nitrogen optionally forms N-oxide or N-chloride.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof,
10 wherein

A is C;
X is benzofuranyl;
R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or
-C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6
15 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂₋C₁₋₆alkyl;
R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-
20 phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-
25 O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(
30 C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl.

5 6cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
10 optionally, R₂ forms =O with an adjoining bond;
 R₄ is hydrogen, or halogen; and
 any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In yet another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

15 A is C;
X is pyridyl;
R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or
-C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6
substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂₋

20 C₁₋₆alkyl;
R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)2, -C₀₋₄alkyl(C₃₋₆cycloalkyl)2, -C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)2, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₆alkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl,

- C₀-4alkyl)(O-C₀-4alkyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -S-C₁-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-C₀-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-N(C₀-6alkyl)2, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -SO₂-N(C₀-4alkyl)2, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₁-4alkyl-Si(C₀-4alkyl)3, -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, or -C₀-4alkyl-S-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl;
- R₄ is hydrogen, or halogen; and
any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In yet still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

- A is C;
X is pyridyl;
R₁ is hydrogen, halogen; or -C₁-6alkyl, -cycloC₃-6alkyl, or -C₁-6alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁-6alkyl;
R₃ is hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁-6alkyl, -C₂-6alkenyl, -C₁-6alkyl(C₂-6alkenyl)2, -C₀-4alkyl(C₃-6cycloalkyl)2, -C₀-6alkyl-N(C₀-6alkyl)2, -C₀-4alkyl-O-C₁-6alkyl, -C₁-6alkyl-phenyl, -C₀-6alkyl-SO₂-C₁-6alkyl, -C₀-6alkyl-C(O)-C₀-4alkyl, -C₀-6alkyl-C(O)-C₀-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-4alkyl-O-C₀-6alkyl, -C₀-6alkyl-C(O)-C₀-6alkyl-O-C₀-6alkyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl-N(C₀-6alkyl)2, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-4alkyl-O-C₀-6alkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)2, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl,

6cycloalkyl, $-\text{SO}_2\text{C}_0\text{-}6\text{alkyl-phenyl}$, $-\text{SO}_2\text{C}_0\text{-}6\text{alkyl}\text{(-C}_0\text{-}6\text{alkyl-phenyl)(-C}_0\text{-}6\text{alkyl-phenyl)}$, $-\text{C}_0\text{-}4\text{alkyl-SO}_2\text{C}_0\text{-}4\text{alkyl-C}_3\text{-}6\text{cycloalkyl-C}_0\text{-}4\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl-O-C}_0\text{-}4\text{alkyl}$, $-\text{S(O)-C}_0\text{-}6\text{alkyl}$, $-\text{P(O)(O-C}_0\text{-}4\text{alkyl)(O-C}_0\text{-}4\text{alkyl)}$, $-\text{C}_2\text{-6alkenyl-C(O)-C}_0\text{-}4\text{alkyl-N(C}_0\text{-}4\text{alkyl)-pyridyl}$, $-\text{S-C}_1\text{-6alkyl}$, $-\text{C}_0\text{-}6\text{alkyl-N(C}_0\text{-}6\text{alkyl)-C(O)-C}_0\text{-}6\text{alkyl-N(C}_0\text{-}6\text{alkyl)2}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_1\text{-4alkyl-oxadiazolyl(C}_0\text{-}4\text{alkyl)}$, $-\text{C}_0\text{-}4\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl-phenyl}$, $-\text{C}_0\text{-}4\text{alkyl-O-C}_0\text{-}4\text{alkyl-phenyl}$, $-\text{C}_0\text{-}4\text{alkyl-C}_3\text{-}6\text{cycloalkyl-C}_0\text{-}4\text{alkyl-tetrazolyl}$, $-\text{SO}_2\text{N(C}_0\text{-}4\text{alkyl)2}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_0\text{-}4\text{alkyl-thiadiazolyl(C}_0\text{-}4\text{alkyl)}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_0\text{-}4\text{alkyl-diazolyl(C}_0\text{-}4\text{alkyl)}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_1\text{-4alkyl-Si(C}_0\text{-}4\text{alkyl)3}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_0\text{-}4\text{alkyl-phenyl(C}_0\text{-}4\text{alkyl)}$, $-\text{C}_0\text{-}4\text{alkyl-S-C}_0\text{-}4\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl-O-C}_0\text{-}4\text{alkyl}$, or $-\text{C}_0\text{-}4\text{alkyl-S-C}_0\text{-}4\text{alkyl-C}_3\text{-}6\text{cycloalkyl-C}_0\text{-}4\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl-O-C}_0\text{-}4\text{alkyl}$, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, $-\text{C}_0\text{-}4\text{alkyl-O-C}_1\text{-6alkyl}$, or $-\text{C}_0\text{-}4\text{alkyl-S-C}_1\text{-6alkyl}$;

15 R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and

any ring nitrogen optionally forms N-oxide or N-chloride.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

A is C;

X is quinolinyl;

R₁ is hydrogen, halogen; or $-\text{C}_1\text{-6alkyl}$, $-\text{cycloC}_3\text{-6alkyl}$, or

25 $-\text{C}_1\text{-6alkenyl group}$, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or $-\text{SO}_2\text{C}_1\text{-6alkyl}$;

30 R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, $-\text{NO}_2$; or $-\text{C}_1\text{-6alkyl}$, $-\text{C}_2\text{-6alkenyl}$, $-\text{C}_1\text{-6alkyl(C}_2\text{-6alkenyl)2}$, $-\text{C}_0\text{-}4\text{alkyl(C}_3\text{-}6\text{cycloalkyl)2}$, $-\text{C}_0\text{-}6\text{alkyl-N(C}_0\text{-}6\text{alkyl)2}$, $-\text{C}_0\text{-}4\text{alkyl-O-C}_1\text{-6alkyl}$, $-\text{C}_1\text{-6alkyl-phenyl}$, $-\text{C}_0\text{-}6\text{alkyl-SO}_2\text{C}_1\text{-6alkyl}$, $-\text{C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl}$, $-\text{C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}6\text{alkyl-phenyl}$, $-\text{C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}4\text{alkyl-O-C}_0\text{-}6\text{alkyl}$, $-\text{C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}6\text{alkyl-O-C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}6\text{alkyl}$, $-\text{C}_2\text{-6alkenyl-C(O)-C}_0\text{-}4\text{alkyl-O-C}_0\text{-}6\text{alkyl}$, $-\text{C}_0\text{-}4\text{alkyl-C}_3\text{-}6\text{cycloalkyl-C}_0\text{-}6\text{alkyl-C(O)-C}_0\text{-}6\text{alkyl}$, $-\text{C}_0\text{-}4\text{alkyl-}$

C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl-N(C₀-6alkyl)₂, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-4alkyl-O-C₀-6alkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)₂, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₀-4alkyl-SO₂-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, -S(O)-C₀-6alkyl, -P(O)(O-C₀-4alkyl)(O-C₀-4alkyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -S-C₁-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-C₀-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-N(C₀-6alkyl)₂, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -SO₂-N(C₀-4alkyl)₂, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₁-4alkyl-Si(C₀-4alkyl)₃, -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, or -C₀-4alkyl-S-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl; optionally, R₂ forms =O with an adjoining bond;

20 R₄ is hydrogen, or halogen; and any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

25 A is C;
X is oxadiazolyl;
R₁ is hydrogen, halogen; or -C₁-6alkyl, -cycloC₃-6alkyl, or -C₁-6alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁-6alkyl;

30 R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁-6alkyl, -C₂-6alkenyl, -C₁-6alkyl(C₂-6alkenyl)₂, -C₀-4alkyl(C₃-6cycloalkyl)₂, -C₀-6alkyl-N(C₀-6alkyl)₂, -C₀-4alkyl-O-C₁-6alkyl, -C₁-6alkyl-

phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-

5 C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₆alkyl-O-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(

10 C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₀₋₄alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;

15 optionally, R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and

any ring nitrogen optionally forms N-oxide or N-chloride.

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In yet another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

30 A is C;
X is diazolylpyridinyl or imidazolylpyridinyl;
R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6

substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁₋₆alkyl;

- R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)2, -C₀₋₄alkyl(C₃₋₆cycloalkyl)2, -C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)2, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl(-C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)2, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)3, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
- optionally, R₂ forms =O with an adjoining bond;
- R₄ is hydrogen, or halogen; and
- any ring nitrogen optionally forms N-oxide or N-chloride.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

- A is C;
- X is pyrazinyl;
- R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or
-C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6
5 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂₋
C₁₋₆alkyl;
- R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)2, -C₀₋₄alkyl(C₃₋₆cycloalkyl)2, -C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-
10 phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-C₃₋₁₅cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)2, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(
20 C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)2, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₂₅cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)2, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)3, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₃₀alkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
optionally, R₂ forms =O with an adjoining bond;
R₄ is hydrogen, or halogen; and
any ring nitrogen optionally forms N-oxide or N-chloride.

In yet still another embodiment of this one aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

- A is C;
- 5 X is oxadiazolylphenyl;
- R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁₋₆alkyl;
- 10 R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀₋₄alkyl-O-C₁₋₆alkyl, or -C₀₋₄alkyl-S-C₁₋₆alkyl;
- 30 35 optionally, R₂ forms =O with an adjoining bond;

R₄ is hydrogen, or halogen; and
any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In even another embodiment of this one aspect, the compound of this
5 invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof,
wherein

- A is C;
- X is benzodioxolyl;
- R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or
- 10 -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6
substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂₋
C₁₋₆alkyl;
- R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(
25 -C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-C(O)-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-O-C₀₋₄alkyl-phenyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-tetrazolyl, -SO₂-N(C₀₋₄alkyl)₂, -C₀₋₄alkyl-S-C₀₋₄alkyl-thiadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-diazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₁₋₄alkyl-Si(C₀₋₄alkyl)₃, -C₀₋₄alkyl-S-C₀₋₄alkyl-phenyl(C₀₋₄alkyl), -C₀₋₄alkyl-S-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, or -C₀₋₄alkyl-S-C₀₋₄alkyl-C₃₋₆
- 30

$\text{6cycloalkyl-C}_0\text{-4alkyl-C(O)-C}_0\text{-4alkyl-O-C}_0\text{-4alkyl}$, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, $-\text{C}_0\text{-4alkyl-O-C}_1\text{-6alkyl}$, or $-\text{C}_0\text{-4alkyl-S-C}_1\text{-6alkyl}$;
 optionally, R₂ forms =O with an adjoining bond;
 R₄ is hydrogen, or halogen; and
 any ring nitrogen optionally forms *N*-oxide or *N*-chloride.

In a second aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

10 A is N;
X is phenyl, pyridyl, pyrazinyl, thiaphenyl, quinolinyl, benzofuranyl, oxadiazolyl, diazolylpyridinyl, imidazolylpyridinyl, oxadiazolylphenyl, or benzodioxolyl;

15 R₁ is hydrogen, halogen; or -C₁₋₆alkyl, -cycloC₃₋₆alkyl, or -C₁₋₆alkenyl group, wherein any of the groups is optionally substituted with 1-6 substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-C₁₋₆alkyl;

20 R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, -NO₂; or -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₁₋₆alkyl(C₂₋₆alkenyl)₂, -C₀₋₄alkyl(C₃₋₆cycloalkyl)₂, -C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-O-C₁₋₆alkyl, -C₁₋₆alkyl-phenyl, -C₀₋₆alkyl-SO₂-C₁₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-phenyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₆alkyl-C(O)-C₀₋₆alkyl-O-C₀₋₆alkyl-O-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₆alkyl-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₆alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₆alkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₆alkyl)-pyridyl, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)₂, -C₀₋₆alkyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-C₃₋₆cycloalkyl, -SO₂-C₀₋₆alkyl-phenyl, -SO₂-C₀₋₆alkyl-(C₀₋₆alkyl-phenyl)(-C₀₋₆alkyl-phenyl), -C₀₋₄alkyl-SO₂-C₀₋₄alkyl-C₃₋₆cycloalkyl-C₀₋₄alkyl-C(O)-C₀₋₄alkyl-O-C₀₋₄alkyl, -S(O)-C₀₋₆alkyl, -P(O)(O-C₀₋₄alkyl)(O-C₀₋₄alkyl), -C₂₋₆alkenyl-C(O)-C₀₋₄alkyl-N(C₀₋₄alkyl)-pyridyl, -S-C₁₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-C₀₋₆alkyl, -C₀₋₆alkyl-N(C₀₋₆alkyl)-C(O)-N(C₀₋₆alkyl)₂, -C₀₋₄alkyl-S-C₁₋₄alkyl-oxadiazolyl(C₀₋₄alkyl), -C₀₋₄alkyl-

C(O)–C₀–alkyl–phenyl, –C₀–alkyl–O–C₀–alkyl–phenyl, –C₀–alkyl–C₃–6cycloalkyl–C₀–alkyl–tetrazolyl, –SO₂–N(C₀–alkyl)₂, –C₀–alkyl–S–C₀–alkyl–thiadiazolyl(C₀–alkyl), –C₀–alkyl–S–C₀–alkyl–diazolyl(C₀–alkyl), –C₀–alkyl–S–C₁–alkyl–Si(C₀–alkyl)₃, –C₀–alkyl–S–C₀–alkyl–phenyl(C₀–alkyl), –C₀–

In an embodiment of the second aspect, the compound of this invention is represented by Formula (I), or a pharmaceutically acceptable salt thereof, wherein

- 15 A is N;
X is phenyl;
R₁ is hydrogen, halogen; or -C₁-6alkyl, -cycloC₃-6alkyl, or
-C₁-6alkenyl group, wherein any of the groups is optionally substituted with 1-6
substituents; wherein each substituent is independently halogen, -OH, -CN, or -SO₂-

20 C₁-6alkyl;
R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN,
-NO₂; or -C₁-6alkyl, -C₂-6alkenyl, -C₁-6alkyl(C₂-6alkenyl)2, -C₀-4alkyl(C₃-
6cycloalkyl)2, -C₀-6alkyl-N(C₀-6alkyl)2, -C₀-4alkyl-O-C₁-6alkyl, -C₁-6alkyl-
phenyl, -C₀-6alkyl-SO₂-C₁-6alkyl, -C₀-6alkyl-C(O)-C₀-4alkyl, -C₀-6alkyl-C(O)-
C₀-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-4alkyl-O-C₀-6alkyl, -C₀-6alkyl-C(O)-C₀-
6alkyl-O-C₀-6alkyl-O-C₀-6alkyl-C(O)-C₀-6alkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-
O-C₀-6alkyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl, -C₀-4alkyl-
C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl-N(C₀-6alkyl)2, -C₀-4alkyl-C₃-
6cycloalkyl-C₀-6alkyl-C(O)-C₀-4alkyl-O-C₀-6alkyl, -C₂-6alkenyl-C(O)-C₀-
4alkyl-N(C₀-6alkyl)-pyridyl, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)2, -C₀-
6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -C₂-6alkenyl-C(O)-C₀-
4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(
C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₀-4alkyl-SO₂-C₀-4alkyl-C₃-
6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, -S(O)-C₀-6alkyl, -P(O)(O-

- C₀-4alkyl)(O-C₀-4alkyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -S-C₁-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-C₀-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-N(C₀-6alkyl)2, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -SO₂-N(C₀-4alkyl)2, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₁-4alkyl-Si(C₀-4alkyl)3, -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, or -C₀-4alkyl-S-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl; optionally, R₂ forms =O with an adjoining bond; R₄ is hydrogen, or halogen; and any ring nitrogen optionally forms *N*-oxide or *N*-chloride.
- In one aspect, R₂, and R₃ are each independently hydrogen, halogen, hydroxyl, -CN, or -NO₂.
 In another aspect, R₂, and R₃ are each independently -C₁-6alkyl, -C₂-6alkenyl, -C₁-6alkyl(C₂-6alkenyl)2, or -C₀-4alkyl(C₃-6cycloalkyl)2, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.
 In another aspect, R₂, and R₃ are each independently -C₀-6alkyl-N(C₀-6alkyl)2, -C₀-4alkyl-C₃-6cycloalkyl-C₀-6alkyl-C(O)-C₀-6alkyl-N(C₀-6alkyl)2, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)2, -C₀-6alkyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-C₃-6cycloalkyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-C₀-6alkyl, -C₀-6alkyl-N(C₀-6alkyl)-C(O)-N(C₀-6alkyl)2, or -SO₂-N(C₀-4alkyl)2, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.
 In another aspect, R₂, and R₃ are each independently -C₀-6alkyl-SO₂-C₁-6alkyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-

C₀-6alkyl-phenyl), -C₀-4alkyl- SO₂-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, -S(O)-C₀-6alkyl, -S-C₁-6alkyl, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -SO₂-N(C₀-4alkyl)₂, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₁-4alkyl-Si(C₀-4alkyl)₃, -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, or -C₀-4alkyl-S-C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-C(O)-C₀-4alkyl-O-C₀-4alkyl, wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.

- 5 In an aspect, R₂ forms =O with an adjoining bond;
In another aspect, R₂ and R₃ are each independently -C₁-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-6alkyl-phenyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), or -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.
- 10 In an aspect, R₂ forms =O with an adjoining bond;
In another aspect, R₂ and R₃ are each independently -C₁-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-6alkyl-phenyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), or -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.
- 15 In an aspect, R₂ forms =O with an adjoining bond;
In another aspect, R₂ and R₃ are each independently -C₁-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-6alkyl-phenyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), or -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.
- 20 In an aspect, R₂ forms =O with an adjoining bond;
In another aspect, R₂ and R₃ are each independently -C₁-6alkyl-phenyl, -C₀-6alkyl-C(O)-C₀-6alkyl-phenyl, -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-6alkyl)-pyridyl, -SO₂-C₀-6alkyl-phenyl, -SO₂-C₀-6alkyl-(C₀-6alkyl-phenyl)(-C₀-6alkyl-phenyl), -C₂-6alkenyl-C(O)-C₀-4alkyl-N(C₀-4alkyl)-pyridyl, -C₀-4alkyl-S-C₁-4alkyl-oxadiazolyl(C₀-4alkyl), -C₀-4alkyl-C(O)-C₀-4alkyl-phenyl, -C₀-4alkyl-O-C₀-4alkyl-phenyl, -C₀-4alkyl-C₃-6cycloalkyl-C₀-4alkyl-tetrazolyl, -C₀-4alkyl-S-C₀-4alkyl-thiadiazolyl(C₀-4alkyl), -C₀-4alkyl-S-C₀-4alkyl-diazolyl(C₀-4alkyl), or -C₀-4alkyl-S-C₀-4alkyl-phenyl(C₀-4alkyl), wherein any alkyl, cycloalkyl, alkenyl, phenyl, or pyridyl are each optionally substituted with 1-9 independently halogen, hydroxyl, -C₀-4alkyl-O-C₁-6alkyl, or -C₀-4alkyl-S-C₁-6alkyl.

- 25 In another aspect, the present invention is directed to a method of enhancing cognition in a healthy subject comprising administering a safe cognition enhancing amount of a phosphodiesterase-4 inhibitor. In particular, this invention is directed to a method of enhancing memory, learning, retention, recall, awareness and judgement in health subjects comprising administering a safe and cognition enhancing amount of a phosphodiesterase-4 inhibitor. Within this aspect there is a method of enhancing cognition in a healthy subject comprising administering a safe, non-emetic, cognition enhancing amount of a phosphodiesterase-4 inhibitor
- 30 In another aspect, the present invention is directed to a method of enhancing cognition in a healthy subject comprising administering a safe cognition enhancing amount of a phosphodiesterase-4 inhibitor.

For purposes of this application is defined as a subject with cognition in the normal range for the subjects age or other classification. Cognition of a healthy subject as well as cognition enhancement of the healthy subject is illustrated shown by

testing the compounds in the Morris water maze as reported by McNamara and Skelton, *Psychobiology*, 1993, 21, 101-108. Further details of relevant methodology are described in WO 96/25948. Other assessments for measuring cognition enhancement include, but are not limited to the "T" Maze Test; Radial Arm Maze Test; Delayed Non-Match or Delayed Match Test; Passive Avoidance Procedure; 5 Choice Test, disclosed in WO 01/87281 A2, published November 22, 2001.

For purposes of this specification, classes of healthy subjects includes juveniles, adults and seniors of average cognition; juveniles, adults and seniors of above average cognition; and juveniles, adults and seniors of below average cognition.

For purposes of this specification, juvenile human subjects is defined as a human subject less than 18 years of age. For purposes of this specification, adult human subject is defined as a human subject 18 years of age or older. Within this classification is a human adult 18 to 40 years of age. For purposes of this specification, senior human subjects is defined as a human subject 40 years of age or older. Within this classification is a human subject 55 years of age or older; 65 years of age or older; and 70 years of age or older.

As appreciated by those of skill in the art, beginning at about age 25, the cognition of the healthy human declines at a measurable and reproducible rates, as for example, measured by CAmbridge Neuropsychological Test Automated Battery (CANTAB, de Jager CA, Milwain E, Budge M. Early detection of isolated memory deficits in the elderly: the need for more sensitive neuropsychological tests. *Psychol Med* 2002 Apr;32(3):483-91) or the Cognitive Drug Reseach Battery (CDR, Barker A, Jones R, Simpson P, Wesnes K. (1995). Scopolamine induced cognitive impairment as a predictor of cognitive decline in healthy elderly volunteers. *International Journal of Geriatric Psychiatry* 10: 1059-1062). Thus, by the time a human subject becomes a senior 40 years of age the decline in cognitive function has declined significant and would benefit from a method of memory enhancement.

30

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl,

hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

- The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalenyl, adamantanyl, indanyl, indenyl, fluorenyl, 1,2,3,4-
10 tetrahydronaphthalenyl and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected to the oxy connecting atom.

The term "alkoxy" unless specifically stated otherwise includes an alkyl group connected to the oxy connecting atom.

The term "aryl" unless specifically stated otherwise includes multiple ring systems as well as single ring systems such as, for example, phenyl or naphthyl.

The term "aryloxy" unless specifically stated otherwise includes multiple ring systems as well as single ring systems such as, for example, phenyl or naphthyl, connected through the oxy connecting atom to the connecting site.

The term "C₀-C₆alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminus moiety. An alkyl with no carbon atoms is a direct bond when the alkyl is a bridging moiety.

The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The heteroatoms replace ring carbon atoms. Thus, for example, a heterocycloC₅alkyl is a five membered ring containing from 5 to no carbon atoms.

Examples of heteroaryl include, for example, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl.

The term "heteroaryloxy" unless specifically stated otherwise describes a heteroaryl group connected through an oxy connecting atom to the connecting site.

5 Examples of heteroaryl(C₁₋₆)alkyl include, for example, furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, 10 tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

15 Examples of heterocycloC₃₋₇alkyl include, for example, azetidinyl, pyrrolidinyl, piperidinyl, perhydroazepinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "N-heterocycloC₄₋₇alkyl" describes nonaryl heterocyclic compounds having 3-6 carbon atoms and one nitrogen atom forming the ring. Examples include azetidinyl, pyrrolidinyl, piperidinyl, and perhydroazepinyl.

20 Examples of aryl(C₁₋₆)alkyl include, for example, phenyl(C₁₋₆)alkyl, and naphthyl(C₁₋₆)alkyl.

25 Examples of heterocycloC₃₋₇alkylcarbonyl(C₁₋₆)alkyl include, for example, azetidinyl carbonyl(C₁₋₆)alkyl, pyrrolidinyl carbonyl(C₁₋₆)alkyl, piperidinyl carbonyl(C₁₋₆)alkyl, piperazinyl carbonyl(C₁₋₆)alkyl, morpholinyl carbonyl(C₁₋₆)alkyl, and thiomorpholinyl carbonyl(C₁₋₆)alkyl.

The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines.

Unless otherwise stated, the term "carbamoyl" is used to include -NHC(O)OC_{1-C4}alkyl, and -OC(O)NHC_{1-C4}alkyl.

30 The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, the substitution can be made

at any of the groups. For example, substituted aryl(C₁₋₆)alkyl includes substitution on the aryl group as well as substitution on the alkyl group.

The term "oxide" of heteroaryl groups is used in the ordinary well-known chemical sense and include, for example, *N*-oxides of nitrogen heteroatoms.

5 Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Compounds described herein can contain one or more asymmetric 10 centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all 15 stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be mixtures of stereoisomers.

20 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, 25 ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted 30 amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine,

lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine; purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

- When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are benzenesulfonic, citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drugs ("NSAID"), and ix) M2/M3 antagonists. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.001mg/kg to about 140mg/kg of body weight per day are useful in the treatment of conditions such as i) Pulmonary disorders such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, infant respiratory distress syndrome, cough, chronic obstructive pulmonary disease in animals, adult respiratory distress syndrome, and infant respiratory distress syndrome, ii) Gastrointestinal disorders such

as ulcerative colitis, Crohn's disease, and hypersecretion of gastric acid, iii) Infectious diseases such as bacterial, fungal or viral induced sepsis or septic shock, endotoxic shock (and associated conditions such as laminitis and colic in horses), and septic shock, iv) Neurological disorders such as spinal cord trauma, head injury, neurogenic inflammation, pain, and reperfusion injury of the brain, v) Inflammatory disorders such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, inflammation and cytokine-mediated chronic tissue degeneration, vi) Allergic disorders such as allergic rhinitis, allergic conjunctivitis, and eosinophilic granuloma, vii) Psychiatric disorders such as depression, memory impairment, and monopolar depression, viii) Neurodegenerative disorders such as Parkinson disease, Alzheimer's disease, acute and chronic multiple sclerosis, ix) Dermatological disorders such as psoriasis and other benign or malignant proliferative skin diseases, atopic dermatitis, and urticaria, x) Oncological diseases such as cancer, tumor growth and cancerous invasion of normal tissues, xi) Metabolic disorders such as diabetes insipidus, xii) Bone disorders such as osteoporosis, xiii) Cardiovascular disorders such as arterial restenosis, atherosclerosis, reperfusion injury of the myocardium, and xiv) Other disorders such as chronic glomerulonephritis, vernal conjunctivitis, transplant rejection and graft versus host disease, and cachexia - which are responsive to PDE4 inhibition, or alternatively about 0.05mg to about 7g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01mg to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 2.5g per patient per day. Further, it is understood that the PDE4 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 0.01mg to about 1000mg of the active ingredient, typically 0.01mg, 0.05mg, 0.25mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general

health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral

liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion,

dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or
5 ointment is prepared by mixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the
10 mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the
15 pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a
20 compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as PDE4 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, i)
25 Pulmonary disorders such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, infant respiratory distress syndrome, cough, chronic obstructive pulmonary disease in animals, adult respiratory distress syndrome, and infant respiratory distress syndrome, ii)
Gastrointestinal disorders such as ulcerative colitis, Crohn's disease, and
30 hypersecretion of gastric acid, iii) Infectious diseases such as bacterial, fungal or viral induced sepsis or septic shock, endotoxic shock (and associated conditions such as laminitis and colic in horses), and septic shock, iv) Neurological disorders such as spinal cord trauma, head injury, neurogenic inflammation, pain, and reperfusion injury of the brain, v) Inflammatory disorders such as psoriatic arthritis, rheumatoid arthritis,
35 ankylosing spondylitis, osteoarthritis, inflammation and cytokine-mediated chronic

tissue degeneration, vi) Allergic disorders such as allergic rhinitis, allergic conjunctivitis, and eosinophilic granuloma, vii) Psychiatric disorders such as depression, memory impairment, and monopolar depression, viii) Neurodegenerative disorders such as Parkinson disease, Alzheimer's disease, acute and chronic multiple sclerosis, ix) Dermatological disorders such as psoriasis and other benign or malignant proliferative skin diseases, atopic dermatitis, and urticaria, x) Oncological diseases such as cancer, tumor growth and cancerous invasion of normal tissues, xi) Metabolic disorders such as diabetes insipidus, xii) Bone disorders such as osteoporosis, xiii) Cardiovascular disorders such as arterial restenosis, atherosclerosis, reperfusion injury of the myocardium, and xiv) Other disorders such as chronic glomerulonephritis, vernal conjunctivitis, transplant rejection and graft versus host disease, and cachexia – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cAMP levels – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) COX-2 selective inhibitors, iv) statins, v) NSAIDs, vi) M2/M3 antagonists, vii) corticosteroids, viii) H1 (histamine) receptor antagonists and ix) beta 2 adrenoceptor agonist.

Thus, for example, pulmonary disorders such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, infant respiratory distress syndrome, cough, chronic obstructive pulmonary disease in animals, adult respiratory distress syndrome, and infant respiratory distress syndrome can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

Gastrointestinal disorders such as ulcerative colitis, Crohn's disease, and hypersecretion of gastric acid can be conveniently treated with capsules, cachets

or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

- 5 Infectious diseases such as bacterial, fungal or viral induced sepsis or septic shock, endotoxic shock (and associated conditions such as laminitis and colic in horses), and septic shock can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a
10 pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

Neurological disorders such as spinal cord trauma, head injury, neurogenic inflammation, pain, and reperfusion injury of the brain can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 15 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

- 15 Inflammatory disorders such as psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, inflammation and cytokine-mediated chronic
20 tissue degeneration can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

25 Allergic disorders such as allergic rhinitis, allergic conjunctivitis, and eosinophilic granuloma can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

- 30 Psychiatric disorders such as depression, memory impairment, and monopolar depression can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times
35 daily.

Neurodegenerative disorders such as Parkinson disease, Alzheimer's disease, acute and chronic multiple sclerosis can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

5 Dermatological disorders such as psoriasis and other benign or malignant proliferative skin diseases, atopic dermatitis, and urticaria can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 10 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

15 Oncological diseases such as cancer, tumor growth and cancerous invasion of normal tissues can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

20 Metabolic disorders such as diabetes insipidus can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

25 Bone disorders such as osteoporosis, cardiovascular disorders such as arterial restenosis, atherosclerosis, reperfusion injury of the myocardium, and other disorders such as chronic glomerulonephritis, vernal conjunctivitis, transplant rejection and graft versus host disease, and cachexia can be conveniently treated with capsules, cachets or tablets each containing 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient of the compound of the present 30 application, or a pharmaceutically acceptable salt thereof, administered once, twice, or three times daily.

35 For enhancement of cognition (such as for enhanced memory, learning, retention, recall, awareness and judgement), dosage levels from about 0.0001mg/kg to about 50mg/kg of body weight per day are useful or about 0.005mg to about 2.5g per patient per day. Alternatively, dosage levels from about 0.001mg to

10mg of the compound per kilogram of body weight per day, or alternatively about 0.05mg to about 500mg per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.005mg to about 2.5g of active agent, compounded with an appropriate and convenient amount of carrier materia. Unit dosage forms will generally contain between from about 0.005mg to about 1000mg of the active ingredient, typically 0.005, 0.01mg, 0.05mg, 0.25mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg, administered once, twice or three times a day.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et ₃ N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide

LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt 6H ₂ O
Ms	methanesulfonyl = mesyl = SO ₂ Me
MsO	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	2KHSO ₅ •KHSO ₄ •K ₂ SO ₄
PCC	pyridinium chlorochromate
Pd ₂ (dba) ₃	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO ₂ NH ₂
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl

XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C ₃ H ₅	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

5

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY**LPS AND FMLP-INDUCED TNF- α AND LTB₄ ASSAYS IN HUMAN WHOLE BLOOD**

- 10 Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF- α and LTB₄. Upon stimulation with LPS, activated monocytes express and secrete TNF- α up to 8 hours and plasma levels remain stable for 24 hours.
- 15 Published studies have shown that inhibition of TNF- α by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB₄ synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE4-selective inhibitors. As there is little LTB₄

produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB₄ synthesis by activated neutrophils. Thus, by using the same blood sample, it is possible to evaluate the potency of a compound on two surrogate markers of PDE4 activity in the whole blood by the following procedure.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. 500 μ L aliquots of blood were pre-incubated with either 2 μ L of vehicle (DMSO) or 2 μ L of test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 μ L vehicle (PBS) as blanks or 10 μ L LPS (1 μ g/mL final concentration, #L-2630 (Sigma Chemical Co., St. Louis, MO) from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 μ L of PBS (blank) or 10 μ L of LPS (1 μ g/mL final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 μ L of PBS (blank) or 10 μ L of fMLP (1 μ M final concentration, #F-3506 (Sigma); diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50 μ L aliquot of plasma was mixed with 200 μ L methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB₄ using an enzyme immunoassay kit (#520111 from Cayman Chemical Co., Ann Arbor, MI) according to the manufacturer's procedure. TNF- α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology, Pine Brook, NJ) according to manufacturer's procedure. IC₅₀ values should be less than about 5 μ M, advantageously less than about 2.5 μ M. The IC₅₀ values of Examples 1 to 155 ranged from 0.005 μ M to 36 μ M.

ANTI-ALLERGIC ACTIVITY IN VIVO

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Guinea pigs were initially sensitized to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminum hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later. At six weeks, animals were challenged with aerosolized ovalbumin while under cover of an intraperitoneally

administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of 5 the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the accumulation of other inflammatory leukocytes.

SPA BASED PDE ACTIVITY ASSAY PROTOCOL

10 Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format as follows:

15 In a 96 well-plate at 30°C the test compound was added (dissolved in 2µL DMSO), 188µL of substrate buffer containing [2,8-³H] adenosine 3',5'-cyclic phosphate (cAMP, 100nM to 50µM), 10mM MgCl₂, 1mM EDTA, 50mM Tris, pH 7.5. The reaction was initiated by the addition of human recombinant PDE4 (the amount was controlled so that ~10% product was formed in 10min.). The reaction was stopped after 10min. by the addition of 1mg of PDE-SPA beads (Amersham Pharmacia Biotech, Inc., Piscataway, NJ). The product AMP generated was 20 quantified on a Wallac Microbeta® 96-well plate counter (EG&G Wallac Co., Gaithersburg, MD). The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC₅₀ value was approximated with a non-linear regression fit 25 using the standard 4-parameter/multiple binding sites equation from a ten point titration.

30 The IC₅₀ values of Examples 1 to 155 were determined with 100nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. IC₅₀ values should be less than about 1000nM, advantageously less than about 250nM, and even more advantageously less than about 100nM. The IC₅₀ values of Examples 1 to 155 ranged from 0.086 nM to 160 nM.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-
5 4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with
10 different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. Yields are given for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 15 500 MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling
20 point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

METHODS OF SYNTHESIS

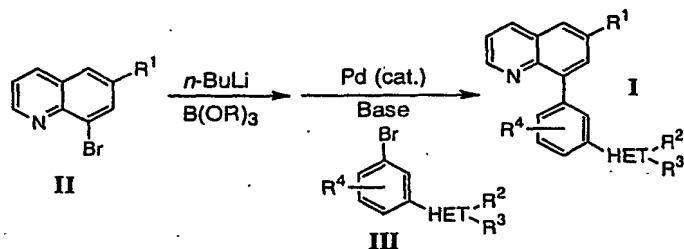
Compounds of the present invention can be prepared according to the
25 following general methods. Reactions are typically run under nitrogen atmosphere at ambient temperature if not otherwise mentioned. Anhydrous solvent such as THF, DMF, Et₂O, DME and Tol are commercial grade. Reagents are commercial grade and were used without any purification. Flash chromatography is run on silica gel (230-400 mesh).

30 All 8-aryl-quinoline of the type I were prepared (**SCHEME 1** and **SCHEME 2**) using a Suzuki coupling to build the biaryl moiety. In a typical Suzuki coupling reaction, all reagents except for the palladium catalyst are mixed in the appropriate solvent. The mixture is then degassed (-O₂) by refluxing for 15 min under nitrogen atmosphere, then cooling to rt, or by applying two to three vacuum/nitrogen

sequences. The palladium catalyst is then added and the reaction mixture is stirred at the appropriate temperature until completion as monitored by TLC.

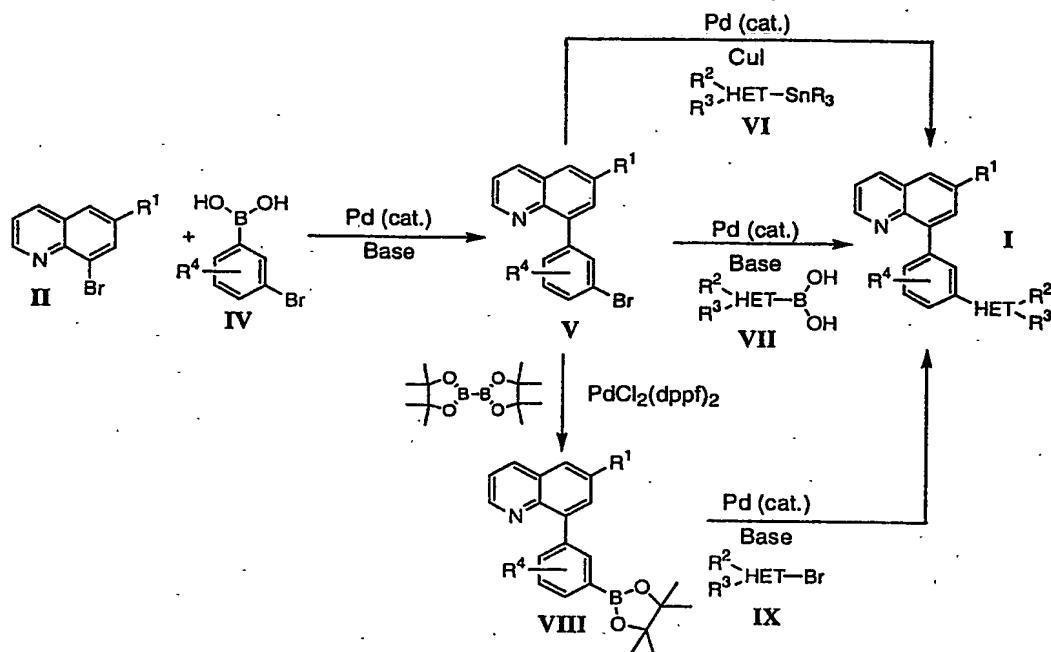
- The substituents are the same as in Formula I except where defined otherwise. Compounds of the type I (**SCHEME 1**) can be prepared in a two step one-pot manner by generating *in-situ* the boronate analog of 8-bromo quinoline II followed by a palladium catalyzed coupling with the appropriate biaryl III

SCHEME 1



- In most cases, compounds were prepared by the two procedures described in **SCHEME 2**. A Suzuki coupling between the 8-bromo-quinoline II and the bromo-phenyl-boronic acid IV produced to the common intermediate V. The latter can be coupled with either an aryl-stannane of type VI or a boronic acid of type VII to generate the desired compound I. Alternatively, the arylbromide V can be converted to the corresponding pinacole boronate VIII by a $PdCl_2(dppf)_2$ catalyzed coupling reaction with pinacole diborane. Subsequently, a Suzuki coupling of the boronate VIII with the appropriate heteroaryl bromide IX will generate the desired compound I

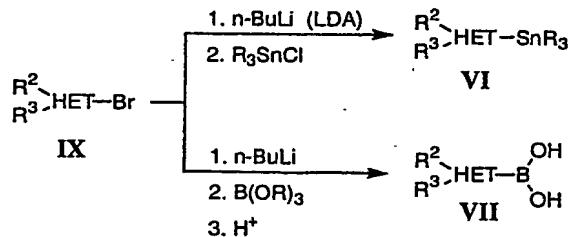
SCHEME 2



Boronic acid of the type VII can be prepared (SCHEME 3) by lithium-halogen exchange at low temperature in THF or Et₂O on the corresponding 5 heteroaryl bromide IX followed by the addition of a trialkyl-boronate (B(OR)₃). Hydrolysis, under acidic condition, of the resulting heteroaryl-boronate will generate the desired boronic acid VII. Likewise, lithium-halogen exchange or deprotonation at low temperature in THF or Et₂O followed by the addition of a trialkylstannyl-chloride (R₃SnCl) generates the stannane of type VI.

10

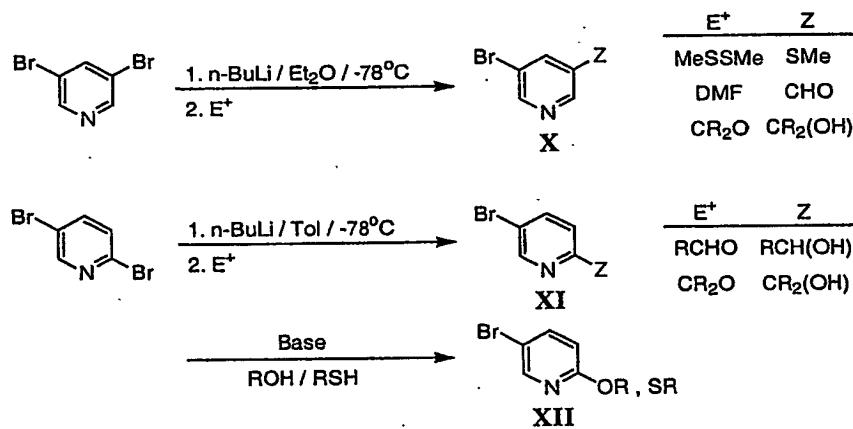
SCHEME 3



Intermediate of the type X can be generated by a mono lithium-halogen exchange at low temperature in ether followed by addition of various electrophiles as

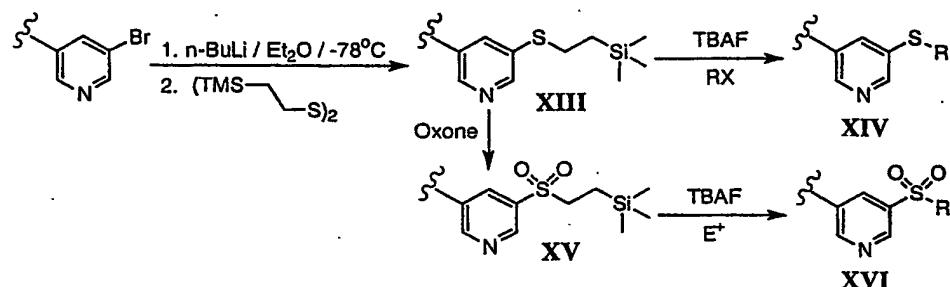
exemplified in SCHEME 3a. Intermediate of the type XI can be generated by a selective mono lithium-halogen exchange at the 2 position in toluene at low temperature followed by addition of various electrophils as exemplified in SCHEME 3a. Intermediate of the type XII can be prepared by a selective nucleophilic displacement by using the sodium salt generated in DMF of various alcohols and mercaptans as exemplified in SCHEME 3a.

SCHEME 3a

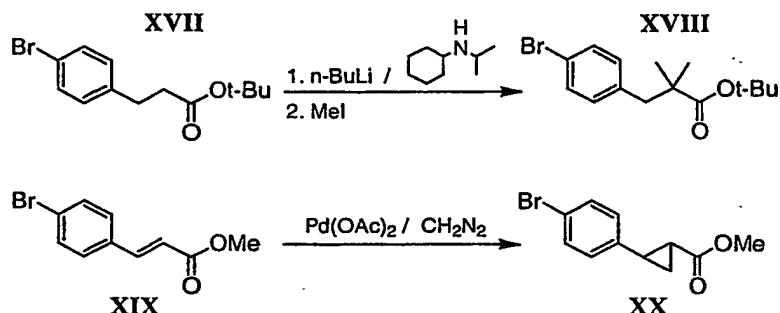


Intermediate of the type XIV can be generated in two steps by first, lithium-halogen exchange at low temperature in ether followed by addition of 1-trimethylsilyl-2-(2-trimethylsilyl-ethyldisulfanyl)-ethane to yield the thio-ether XIII. Secondly, upon addition of TBAF to XIII the thio-phenolate is formed and addition of the electrophile RX will generate the desired intermediate XIV. A similar reaction can be achieved on the sulfone XV, which will generate a nucleophilic sulfinate upon addition of TBAF.

SCHEME 4



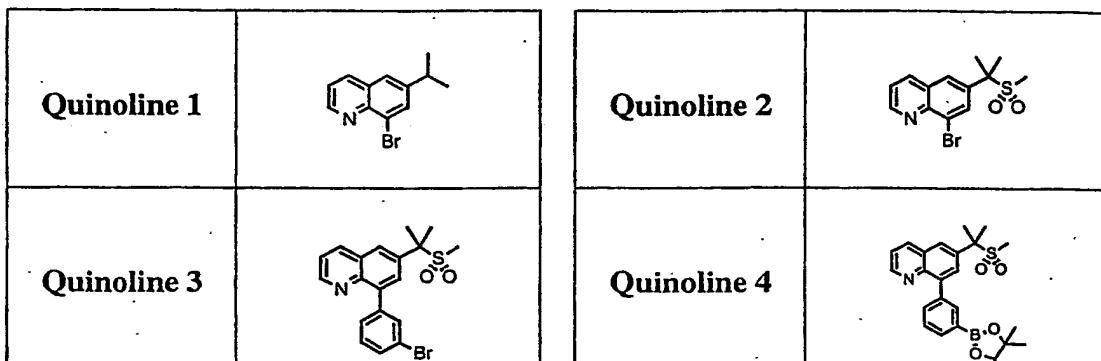
Intermediates such as XVIII are prepared from the steric hindered ester XVII. Deprotonation using lithium *iso*-propyl-cyclohexylamine (1eq.) followed by addition 5 of MeI affords the mono alkylated analog. Repeating several time the same procedure will finally give the desired ester XVIII. The cyclopropyl ester XX can be prepared by a palladium catalyzed cyclopropanation using diazomethane.



10 All the intermediates used for the preparation of the following compounds are commercially available or are prepared according to the litterature. The quinoline intermediates in Table 1 were prepared using the following procedures.

Table 1

Compound	Structure	Compound	Structure
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**Quinoline 1****8-Bromo-6-isopropyl-quinoline**

The preparation of Quinoline 1 is described in International
5 Patent Publication WO 94/22852.

Quinoline 2**8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline****Step 1: 8-Bromo-6-methanesulfonylmethyl-quinoline**

10 To a solution of 6-bromomethyl-8-bromoquinoline (1.0eq.) described in International Patent Publication WO 94/22852 in DMF, was added sodium methanesulfinate (1.4eq.). After stirring overnight at rt, the mixture was quenched with H₂O, stirred for 1h. The resulting precipitate was isolated by filtration and washed with Et₂O to afford the title compound.

15 Step 2: Quinoline 2

To a solution of 8-bromo-6-methanesulfonylmethyl-quinoline from Step 1 (1eq.) in THF (0.2M) at 0°C, was added potassium *t*-butoxide (1.3eq.) over 30min. After 0.5h at 0°C, MeI (1.6eq.) was added and the reaction mixture was stirred at 0°C for 2h. A second portion of potassium *t*-butoxide (1.3eq.) was added over 30min, followed by MeI (1.6eq.). The final mixture was stirred at rt for 2h. The mixture was poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was vigorously stirred in Et₂O and the title compound was isolated by filtration as a pale yellow solid.

25

Quinoline 3**8-(3-Bromo-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**

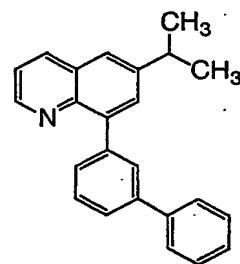
A mixture of **Quinoline 2** (1.0eq.), 3-bromo phenylboronic acid (1.05eq), Na₂CO₃ (2M in H₂O; 3.6eq.) and Pd(PPh₃)₄ (0.03eq.) in DME (0.2M) was stirred at 80°C for 8h. The resulting mixture was cooled to rt and diluted with water under vigorous stirring. The resulting precipitate was filtered and dried. Flash chromatography (Hex:EtOAc; 2:3) and stirring in a mixture of Et₂O and CH₂Cl₂ (10:1) yielded the title compound as a light yellow solid after filtration.

10

Quinoline 4**6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-quinoline**

A mixture of **Quinoline 3** (1.0eq.), pinacole diborane ester(1.4eq) and KOAc (3.5eq.) and PdCl₂(dppf)₂ (0.03eq.) in DMF (0.14M) was stirred at 60°C for 24h. An extra amount of pinacole diborane (0.3eq), KOAc (1.05eq.) and PdCl₂(dppf)₂ (0.01eq.) were added and the mixture was stirred at 60°C for 24h. The resulting mixture was cooled to rt, diluted with EtOAc:Et₂O (1:1). The organic phase was washed with water (3x), brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂:EtOAc; 9:1) and stirring in Et₂O:EtOAc (10:1) afforded the title compound as a white solid.

20

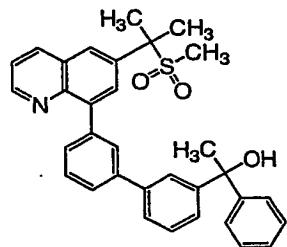
EXAMPLE 1**8-Biphenyl-3-yl-6-isopropyl-quinoline**

25

To a solution of **Quinoline 1** (1.0eq.) in Et₂O (0.1M) at -78°C was added dropwise *sec*-BuLi (1.0eq.). The mixture was stirred for 15min then tri-isopropyl boronate (1.1 eq.) was added. The final mixture was warm to rt and

concentrated. To the residue was added 3-bromo-1,1' biphenyl (1.5eq.), Na₂CO₃ (2M in H₂O; 3.5eq.) and Pd(PPh₃)₄ (0.05eq.) in Tol:EtOH (1:1, 0.2M). The mixture was stirred at 80°C for 12h, cooled to rt, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc ; 9:1) afforded the title compound as an oil. ¹H NMR (400 MHz, acetone-d₆): δ 8.82 (dd, 1H), 8.32 (dd, 1H), 7.99 (t, 1H), 7.81 (m, 2H), 7.75-7.66 (m, 4H), 7.55 (t, 1H), 7.5-7.45 (m, 3H), 7.36 (t, 1H), 3.21 (m, 1H), 1.39 (d, 6H).

10

EXAMPLE 2**1-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-1-phenyl-ethanol**

15 **Step 1:** 1-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-ethanone

A mixture of Quinoline 3 (1.0eq.), (3-acetyl-phenyl)-boronic acid (1.5eq.), Na₂CO₃ (3.0eq.; 2M in H₂O) and PdCl₂(dpff)₂ (0.05eq.) in *n*-propanol (0.2M) was stirred at 80°C for 2h. The mixture was cooled to rt, poured in brine and extracted with EtOAc (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc ; 9:1 to 1:9 over 20 min) afforded the title compound as a yellow solid.

Step 2: EXAMPLE 2

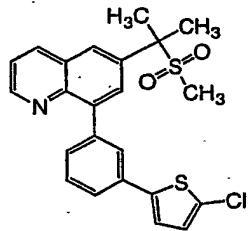
To a solution of 1-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-ethanone from Step 1 (1.0eq.) in THF (0.1M) was added CeCl₃ (1.1eq.). The mixture was put in an ultrasonic bath for 15min, cooled to -78°C then phenyl magnesium bromide was added (5.0eq.). The final mixture was stirred for 12h at -20°C, poured in NaHCO₃ and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash

chromatography (Hex:EtOAc ; 9:1 to 1:9 over 20min) afforded the title compound as a white solid. ¹H NMR (400 MHz, acetone-*d*₆): δ 8.91 (dd, 1H), 8.46 (dd, 1H), 8.29 (d, 1H), 8.18 (d, 1H), 7.97 (d, 1H), 7.86 (d, 1H), 7.68 (dd, 1H), 7.64 (dd, 1H), 7.59-7.50 (m, 5H), 7.48 (d, 1H), 7.39 (t, 1H), 7.27 (t, 2H), 7.16 (t, 1H), 4.73 (s, 1H), 2.72 (s, 3H), 1.99 (s, 6H), 1.98 (s, 3H).

5

EXAMPLE 3

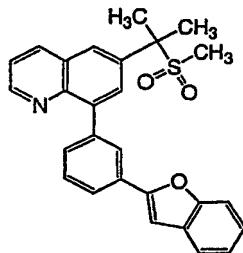
8-[3-(5-Chloro-thiophen-2-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



10

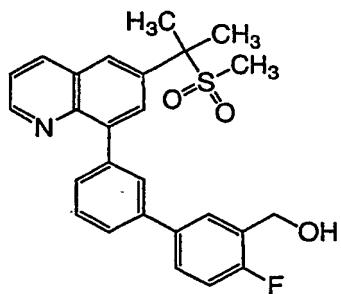
A mixture of Quinoline 4 (1.0eq.), 2-bromo-3-chloro-thiophene (2.0eq.), Na₂CO₃ (3.0eq.; 2M in H₂O) and PdCl₂(dpff)₂ (0.05eq.) in DME (0.2M) was stirred at 80°C for 12h. The mixture was cooled to rt and concentrated. Flash chromatography (Hex:EtOAc; 9:1 to 1:9 over 20 min) afforded the title compound as a yellow solid. ¹H NMR (400 MHz, acetone-*d*₆): δ 8.93 (dd, 1H), 8.47 (dd, 1H), 8.3 (d, 1H), 8.19 (d, 1H), 7.97 (t, 1H), 7.69-7.64 (m, 2H), 7.60-7.52 (m, 2H), 7.35 (d, 1H), 7.07 (d, 1H), 2.72 (s, 3H), 2.00 (s, 6H).

15

EXAMPLE 4**8-(3-Benzofuran-2-yl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**

A mixture of **Quinoline 3** (1.0eq.), 2-benzofuran boronic acid (1.2eq.),

- 5 Na_2CO_3 (2.5eq.; 2M in H_2O) and $\text{Pd}(\text{PPh}_3)_4$ (0.05eq.) in DME (0.1M) was stirred at 80°C for 12h. The mixture was cooled to rt, poured in saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (Hex:EtOAc ; 9:1 to 1:9 in 20min) afforded the title compound as a yellow solid. ^1H NMR (500 MHz, acetone- d_6): δ 8.93 (dd, 1H), 8.47 (dd, 1H), 8.30 (dd, 2H), 8.21 (s, 1H), 7.98 (dd, 1H), 7.75-7.55 (m, 5H), 7.30 (m, 2H), 7.25 (t, 1H), 2.73 (s, 3H), 2.01 (s, 6H).
- 10

EXAMPLE 5**{4-Fluoro-3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-methanol****Step 1: 5-Bromo-2-fluoro-benzylalcohol**

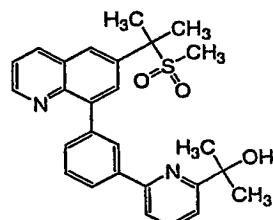
- To a solution of 5-bromo-2-fluoro-benzaldehyde (1.0eq.) in MeOH (0.2M) at 0°C was added portionwise NaBH_4 (2.0eq.). The mixture was stirred at rt for 1h, poured in HCl (1M) and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford the title compound as a white solid.

Step 2: 4-Fluoro-3-hydroxymethyl-phenylboronic acid.

To a solution of 5-bromo-2-fluoro-benzylalcohol (1.0eq.) from Step 1 in THF (0.1M) at -78°C was added dropwise *n*-BuLi (2.2eq.). The mixture was stirred at -78°C for 15min then tri-*isopropylboronate* (2.2eq.) was added. The final 5 mixture was warm slowly to rt, stirred for 1h and quenched with HCl (1M). After stirring for 1h, the mixture was extracted with EtOAc (2x). The combined organic extracts were washed with water, brine, dried over Na₂SO₄, filtered and concentrated. Stirring in Hex:EtOAc:H₂O (90:9:1) for 12h afforded the title compound which was isolated by filtration as a white solid.

10 Step 3: EXAMPLE 5

Prepared according to the procedure described in EXAMPLE 4 but using 4-fluoro-3-hydroxymethyl-phenylboronic acid from Step 2 as starting material. The title compound was obtained as a yellow solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.99 (t, 1H), 7.87 (dd, 1H), 15 7.70-7.55 (m, 5H), 7.17 (t, 1H), 4.75 (d, 2H), 4.38 (t, OH), 2.72 (s, 3H), 1.99 (s, 6H).

EXAMPLE 6**2-(6-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-2-yl)-propan-2-ol**

20

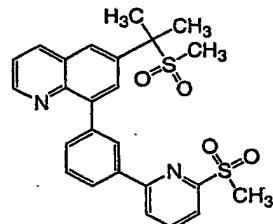
Step 1: 2-(6-Bromo-pyridin-2-yl)-propan-2-ol

To a suspension of 2,6-dibromopyridine (1.0eq.) in Et₂O (0.2M) at -78°C was added dropwise *n*-BuLi (1.05eq.). The mixture was stirred at -78°C for 45min then acetone (1.5eq.) was added. The final mixture was stirred for an extra 25 15min at -78°C and quenched with saturated aqueous NaHCO₃. The mixture was extracted with EtOAc (2x). The combined organic extracts were washed with, brine, dried over MgSO₄, filtered and concentrated to afford the title compound as a white solid which was used as such.

Step 2: EXAMPLE 6

A mixture of **Quinoline 4** (1.0eq.), 2-(6-bromo-pyridin-2-yl)-propan-2-ol (1.2eq.), Na₂CO₃ (3.5eq.; 2M in H₂O), Pd(OAc)₂ (0.05eq.) and PPh₃ (0.15eq.) in *n*-propanol (0.1M) was stirred at 80°C for 15min. The mixture was cooled to rt, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed 5 with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Tol:Ace; 9:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.95 (dd, 1H), 8.53 (t, 1H), 8.48 (dd, 1H), 8.32 (d, 1H), 8.26 (d, 1H), 8.20 (dt, 1H), 7.92-7.81 (m, 3H), 7.65-7.58 (m, 3H), 4.83 (s, OH), 2.76 (s, 3H), 2.03 (s, 6H), 1.58 (s, 6H).

10

EXAMPLE 7**6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methanesulfonyl-pyridin-2-yl)-phenyl]-quinoline**15 **Step 1: 2-Bromo-6-methylsulfanyl-pyridine**

To a solution of 2,6-dibromopyridine (1.0eq.) in DMSO (0.3M) was added sodium methylsulfide (1.1eq.). The mixture was stirred for 2d at rt then poured in water. The resulting precipitate was filtered off and the filtrate was extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated to afford the title compound as a colorless oil. 20 **Step 2: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-2-yl)-phenyl]-quinoline**

25 Prepared according to the procedure described in **EXAMPLE 6, Step 2** but using 2-bromo-6-methylsulfanyl-pyridine as starting material. The title compound was obtained as a light yellow solid.

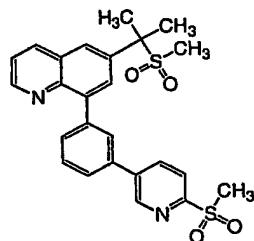
Step 3: EXAMPLE 7

To a solution of 6-(1-methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-2-yl)-phenyl]-quinoline from **Step 2** (1.0eq.) in THF:MeOH: saturated aqueous NaHCO₃ (2:1:1) was added Oxone (2.2eq.). The mixture was

stirred for 12h at rt, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Tol:Acet; 4:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.93 (dd, 1H), 8.55 (t, 1H), 8.46 (dd, 1H), 8.30-8.20 (m, 5H), 7.99 (dd, 1H), 7.89 (dt, 1H), 7.65 (t, 1H), 7.57 (dd, 1H), 3.33 (s, 3H), 2.74 (s, 3H), 2.00 (s, 6H).

EXAMPLE 8

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methanesulfonyl-pyridin-3-yl)-phenyl]-quinoline



Step 1: 3-Bromo-6-methylsulfanyl-pyridine

To a solution of 3,6-dibromopyridine (1.0 eq.) in DMSO (0.3M) was added sodium methylsulfide (1.1eq.). The mixture was stirred for 2d at rt then poured in water. The resulting precipitate was filtered to afford the title compound as white solid.

Step 2: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-3-yl)-phenyl]-quinoline

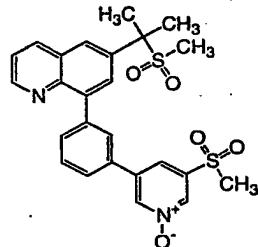
Prepared according to the procedure described in EXAMPLE 6, Step 20 but using 3-bromo-6-methylsulfanyl-pyridine as starting material. The title compound was obtained as a light yellow solid.

Step 3: EXAMPLE 8

Prepared according to the procedure described in EXAMPLE 7, Step 3 but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-3-yl)-phenyl]-quinoline as starting material. The title compound was obtained as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 9.08 (d, 1H), 8.93 (dd, 1H), 8.45 (dd, 1H), 8.41 (dd, 1H), 8.31 (d, 1H), 8.24 (d, 1H), 8.16 (t, 1H), 8.11 (d, 1H), 7.86 (dd, 1H), 7.82 (d, 1H), 7.65 (t, 1H), 7.56 (dd, 1H), 3.26 (s, 3H), 2.73 (s, 3H), 2.00 (s, 6H).

EXAMPLE 9

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methanesulfonyl-1-oxy-pyridin-3-yl)-phenyl]-quinoline



5 Step 1: (5-Methylsulfanyl-pyridin-3-yl)-boronic acid

To a suspension of 3,5-dibromopyridine (1.0eq.) in Et₂O (0.1M) at -78°C was added dropwise *n*-BuLi (1.05eq.). The mixture was stirred at -78°C for 15min then dimethyldisulfide (1.0eq.) was added. The mixture was stirred for 15min and a second portion of *n*-BuLi (1.05eq.) was added. After stirring for 1h at -78°C, tri-*iso*-propylboronate (1.5eq.) was added. The final mixture was warmed slowly to rt and stirred for 12h. An aqueous solution of HCl (1M) was added dropwise until pH=5. The resulting precipitate was filtered to afford the title compound as a white solid, which was used as such.

15 Step 2: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methylsulfanyl-pyridin-3-yl)-phenyl]-quinoline

Prepared according to the procedure described in EXAMPLE 4 but using (5-methylsulfanyl-pyridin-3-yl)-boronic acid as starting material. Upon completion of the reaction (4h), the title compound was isolated by flash chromatography (EtOAc) as a light yellow solid.

20 Step 3: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methanesulfonyl-pyridin-3-yl)-phenyl]-quinoline.

Prepared according to the procedure described in EXAMPLE 7, Step 3, but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methylsulfanyl-pyridin-3-yl)-phenyl]-quinoline from step 2 as starting material. Flash chromatography was not required to get clean material.

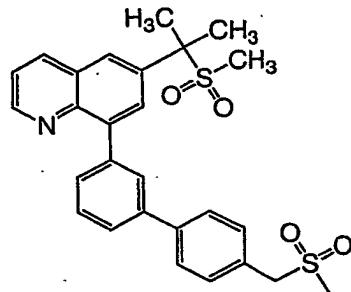
Step 4: EXAMPLE 9

To a solution of 6-(1-methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methanesulfonyl-pyridin-3-yl)-phenyl]-quinoline (1.0eq.) in CH₂Cl₂ (0.1M) was added *m*-CPBA (1.3eq.). The mixture was stirred at rt for 12h, quenched with

Ca(OH)_2 (0.7eq) diluted with CH_2Cl_2 and filtered. The filtrate was concentrated and flash chromatography (EtOAc:MeOH ; 9:1) afforded the title compound as a white solid. $^1\text{H NMR}$ (500 MHz, acetone- d_6): δ 8.95 (dd, 1H), 8.74 (t, 1H), 8.54 (t, 1H), 8.48 (dd, 1H), 8.33 (d, 1H), 8.24 (d, 1H), 8.17 (t, 1H), 8.06 (t, 1H), 7.87 (t, 1H), 7.69 (t, 1H), 7.60 (dd, 1H), 3.40 (s, 3H), 2.75 (s, 3H), 2.02 (s, 6H).

EXAMPLE 10

8-(4'-Methanesulfonylmethyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



10

Step 1: {3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-methanol.

Prepared according to the procedure described in EXAMPLE 4 but using (4-hydroxymethyl-phenyl)-boronic acid as starting material. Flash chromatography (Hex: EtOAc ; 1:1) afforded the title compound as a white solid.

Step 2: 8-(4'-Bromomethyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline.

To a solution of {3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-methanol from Step 1 (1.0eq.) in AcOH (0.3M) was added HBr (48%; 9.5eq.). The mixture was stirred at 80°C for 12h, cooled to rt, poured in cold water containing 10eq. of NaOH and extracted with EtOAc . The organic extract was washed with saturated aqueous NaHCO_3 (3x), brine, dried over Na_2SO_4 , filtered and concentrated to afford the title compound as a yellow solid.

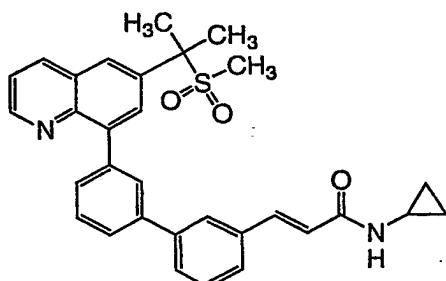
Step 3: EXAMPLE 10

To a solution of 8-(4'-Bromomethyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline (1.0eq.) in DMF (0.1M) was added sodium methanesulfinate (1.3eq.). The mixture was stirred at rt for 2h, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed

with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (Hex:EA ; 1:4) and stirring in EtOAc:Hex:Et₂O (1:7:2) afforded the title compound as a white solid after filtration. ¹H NMR (400 MHz, acetone-*d*₆): δ 8.96 (dd, 1H), 8.49 (dd, 1H), 8.32 (d, 1H), 8.25 (d, 1H), 8.08 (t, 1H), 7.81-7.75 (m, 4H), 7.63-7.59 (m, 4H), 4.48 (s, 2H), 2.90 (s, 3H), 2.75 (s, 3H), 2.03 (s, 6H).

EXAMPLE 11

N-Cyclopropyl-3-[3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-yl]-acrylamide



10

Step 1: 3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-carbaldehyde

Prepared according to the procedure described in EXAMPLE 4 but using (3-Formyl-phenyl)-boronic acid as starting material. Flash chromatography (CH₂Cl₂:EtOAc; 9:1) afforded the title compound as a white solid.

Step 2: 3-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-yl]-acrylic acid

To a solution of 3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-carbaldehyde from Step 1 (1.0eq.) and (dimethoxy-phosphoryl)-acetic acid methyl ester (1.1eq.) in THF (0.1M) was added *t*-BuOK (1.1eq.; 1.0M in THF). The final mixture was stirred 3h at rt, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (CH₂Cl₂:EtOAc; 9:1) afforded the corresponding methyl ester of the title compound as a yellow solid.

To a solution of the methyl ester in THF: MeOH (4:1), aqueous NaOH (3.0eq.) was added. The final mixture was stirred 4h at rt, neutralized with AcOH, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic

extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford the title compound as a white solid.

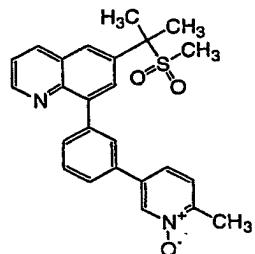
Step 3: EXAMPLE 11

A mixture of 3-[3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-acrylic acid from Step 2 (1.0eq.), EDCI (1.3eq.), DMAP (2.0eq.) and cyclopropylamine (10.0eq.) in CH_2Cl_2 was stirred for 12h at rt. The mixture was poured in saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organic extracts were washed with saturated aqueous NaHCO_3 , brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (EtOAc) afforded the title compound as a white solid. ^1H NMR (500 MHz, acetone- d_6): δ 8.94 (dd, 1H), 8.46 (dd, 1H), 8.30 (d, 1H), 8.24 (d, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.76-7.50 (m, 7H), 7.48 (t, 1H), 7.39 (d, NH), 6.7 (d, 1H), 2.87 (m, 1H), 2.75 (s, 3H), 2.02 (s, 6H), 0.71 (m, 2H), 0.52 (m, 2H).

15

EXAMPLE 12

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methyl-1-oxy-pyridin-3-yl)-phenyl]-quinoline



Step 1: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methyl-pyridin-3-yl)-phenyl]-20 quinoline

To a solution of 5-Bromo-2-methyl-pyridine (1.0eq.) in Et_2O (0.2M) at -78°C was added dropwise *n*-BuLi (1.1eq.). The resulting orange suspension was stirred 15min at -78°C then tri-*iso*-propylboronate (1.8eq.) was added and the final mixture was warmed to 0°C and stirred for 1h. The reaction mixture was quenched with MeOH diluted with Tol and concentrated. To the residue in DME (0.2M) was added Quinoline 3 (0.35eq.), Na_2CO_3 (3.7eq.; aqueous 2M) and $\text{PdCl}_2(\text{dpff})_2$ (0.1eq.). The mixture was stirred at 80°C for 4h, cooled to rt, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with brine,

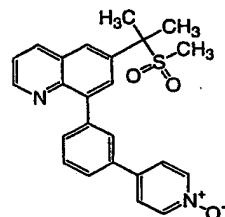
dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (Tol:Acetone; 4:1) afforded the title compound as a light yellow solid.

Step 2: EXAMPLE 12

Prepared according to the procedure described in **EXAMPLE 9, Step 4**, but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methyl-pyridin-3-yl)-phenyl]-quinoline from **Step 1** as starting material. Flash chromatography (EtOAc:MeOH ; 9:1) afforded the title compound as a light yellow solid. ^1H NMR (500 MHz, DMSO- d_6): δ 8.96 (dd, 1H), 8.59 (s, 1H), 8.52 (dd, 1H), 8.29 (d, 1H), 8.08 (d, 1H), 7.97 (d, 1H), 7.79 (dd, 1H), 7.74 (dd, 1H), 7.67-7.60 (m, 3H), 7.57 (d, 1H), 2.82 (s, 3H), 2.41 (s, 3H), 1.95 (s, 6H).

EXAMPLE 13

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(1-oxy-pyridin-4-yl)-phenyl]-quinoline



15

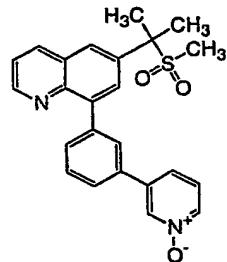
Step 1: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-4-yl-phenyl)-quinoline.

A mixture of **Quinoline 3** (1.0eq.), pyridin-4-yl-boronic acid (1.2eq.), Na_2CO_3 (2.5eq.; 2M in H_2O), $\text{Pd}(\text{PPh}_3)_4$ (0.05eq.) in *n*-propanol (0.1 M) was stirred at 80°C for 4h. The mixture was cooled to rt, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (CH_2Cl_2 :EtOAc ; 1:1) afforded the title compound as a white solid.

Step 2: EXAMPLE 13

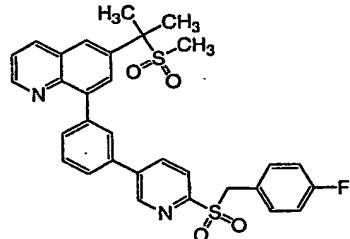
Prepared according to the procedure described in **EXAMPLE 9, Step 4**, but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-4-yl-phenyl)-quinoline from **Step 1** as starting material. Flash chromatography (EtOAc:MeOH ; 4:1) afforded the title compound as a light yellow solid. ^1H NMR (500 MHz, acetone- d_6): δ 8.93 (dd, 1H), 8.52 (dd, 1H), 8.32 (d, 1H), 8.25 (m, 3H), 8.12 (s, 1H), 7.80 (m, 4H), 7.60 (m, 2H), 2.75 (s, 3H), 2.05 (s, 6H).

30

EXAMPLE 14**6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(1-oxy-pyridin-3-yl)-phenyl]-quinoline**

- 5 **Step 1:** 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-3-yl-phenyl)-quinoline
Prepared according to the procedure described in EXAMPLE 13, Step 1, but using pyridin-3-yl-boronic acid as starting material.
- Step 2: EXAMPLE 14**
Prepared according to the procedure described in EXAMPLE 9, Step 10 4, but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-3-yl-phenyl)-quinoline from Step 1 as starting material. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.93 (dd, 1H), 8.49 (s, 1H), 8.47 (dd, 1H), 8.32 (d, 1H), 8.23 (d, 1H), 8.15 (d, 1H), 8.07 (s, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.65 (m, 2H), 7.6 (dd, 1H), 7.48 (t, 1H), 2.75 (s, 3H), 2.05 (s, 6H).

15

EXAMPLE 15**8-{3-[6-(4-Fluoro-phenylmethanesulfonyl)-pyridin-3-yl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**

- 20 **Step 1:** 5-Bromo-2-(4-fluoro-benzylsulfanyl)-pyridine
To a solution of 2,5-dibromopyridine (1.0eq.) and (4-fluoro-phenyl)methanethiol (1.2eq.) in DMF (0.2M) at 0°C was added portionwise NaH (1.3eq.). The mixture was stirred for 1 h at rt, poured in water and extracted with Et₂O. The

organic extract was washed with water (2x), brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc ; 9:1) afforded the title compound as a yellow solid.

Step 2: 5-Bromo-2-(4-fluoro-phenylmethanesulfonyl)-pyridine

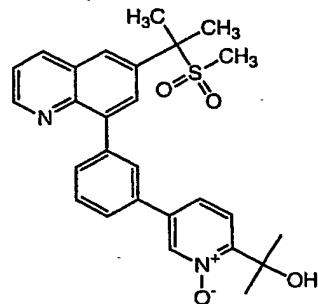
5 Prepared according to the procedure described in EXAMPLE 7, Step 3, but using 5-bromo-2-(4-fluoro-benzylsulfanyl)-pyridine as starting material. Flash chromatography (Hex:EtOAc; 4:1) afforded the title compound as a white solid.

Step 3: EXAMPLE 15

10 Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 5-bromo-2-(4-fluoro-phenylmethanesulfonyl)-pyridine as starting material. The reaction mixture was stirred 2h at 80°C. Flash chromatography (Tol;Ace; 9:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 9.20 (d, 1H), 8.97 (dd, 1H), 8.49 (dd, 1H), 8.37 (dd, 1H), 8.34 (d, 1H), 8.27 (d, 1H), 8.19 (d, 1H), 7.94 (d, 1H), 7.89-7.85 (m, 2H), 7.69 (t, 1H), 7.61 (dd, 1H), 7.37-7.35 (m, 2H), 7.08 (t, 2H), 4.78 (s, 2H), 2.76 (s, 3H), 2.03 (s, 6H).

EXAMPLE 16

2-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-propan-2-ol



20

Step 1: 2-(5-Bromo-pyridin-2-yl)-propan-2-ol

To a suspension of 2,5-dibromopyridine (1.0eq.) in Tol (0.1M) at -78°C was added dropwise *n*-BuLi (1.07eq.). The mixture was stirred at -78°C for 3h then acetone (1.2eq.) was added. The final mixture was stirred for an extra 2h at -78°C, poured in saturated aqueous NH₄Cl and extracted with Tol (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc ; 4:1) afforded the title compound as a white solid.

Step 2: 2-(5-Bromo-1-oxy-pyridin-2-yl)-propan-2-ol

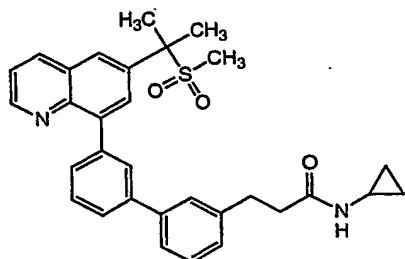
Prepared according to the procedure described in EXAMPLE 9, Step 4, but using 2-(5-bromo-pyridin-2-yl)-propan-2-ol as starting material. Flash chromatography (Hex:EtOAc; 1:1) afforded the title compound as a white solid.

Step 3: EXAMPLE 16

5 Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 2-(5-bromo-1-oxy-pyridin-2-yl)-propan-2-ol as starting material. Flash chromatography (EtOAc) and stirring in Et₂O:EtOAc (9:1) afforded the title compound as a white solid after filtration. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.95 (dd, 1H), 8.71 (d, 1H), 8.54 (dd, 1H), 8.30 (d, 1H), 8.08 (d, 1H), 8.00 (d, 1H), 7.86-10 7.81 (m, 2H), 7.78 (d, 1H), 7.73 (d, 1H), 7.66-7.62 (m, 2H), 7.03 (s, OH), 2.82 (s, 3H), 1.95 (s, 6H), 1.63 (s, 6H).

EXAMPLE 17

15 **N-Cyclopropyl-3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionamide**



Step 1: 3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionic acid methyl ester

To a solution of 3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-acrylic acid methyl ester (1.0 eq.) from EXAMPLE 11, Step 2, in Tol (0.1M) was added benzenesulfonyl hydrazide (3.8 eq.). The mixture was stirred at 100°C for 12h, cooled to rt, poured in saturated aqueous NaHCO₃ and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂:EtOAc; 8.5:1.5) afforded the title compound as a white solid.

Step 2: 3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionic acid

To a solution of 3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionic acid methyl ester (1.0 eq.) from step 1, in THF:MeOH

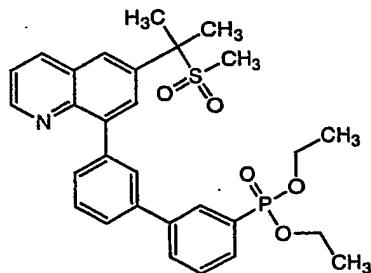
(2:1; 0.2M) was added aqueous LiOH (2M; 4.0eq.). The mixture was stirred for 12h at rt, quenched with AcOH (20eq.), poured in saturated aqueous NH₄OAc and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Crystallization in Hex:CH₂Cl₂ afforded
5 the title compound as a white solid.

Step 3: EXAMPLE 17

Prepared according to the procedure described in EXAMPLE 11, Step 3, but using 3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionic acid from step 2, as starting material. ¹H NMR (500 MHz, acetone-d₆):
10 δ 8.95 (dd, 1H), 8.48 (dd, 1H), 8.32 (d, 1H), 8.23 (d, 1H), 8.02 (s, 1H), 7.71 (m, 2H),
7.60 (m, 4H), 7.38 (t, 1H), 7.23 (d, 1H), 7.05 (s, NH), 2.98 (t, 2H), 2.75 (s, 3H), 2.64
(m, 1H), 2.46 (t, 2H), 2.03 (s, 6H), 0.56 (m, 2H), 0.35 (m, 2H).

EXAMPLE 18

15 {3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-phosphonic acid diethyl ester

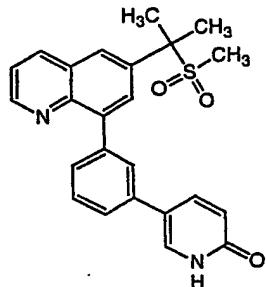


Prepared according to the procedure described in EXAMPLE 6, Step 2, but using (3-bromo-phenyl)-phosphonic acid diethyl ester as starting material.
20 Upon completion of the reaction (1h) the title compound was isolated by flash chromatography (EtOAc) as a light yellow solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.94 (dd, 1H), 8.49 (dd, 1H), 8.32 (d, 1H), 8.28 (d, 1H), 8.12 (d, 1H), 8.10 (s, 1H), 8.0 (d, 1H), 7.85-7.55 (m, 6H), 4.12 (m, 4H), 2.77 (s, 3H), 2.05 (s, 6H), 1.30 (t, 6H).

25

EXAMPLE 19

5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1H-pyridin-2-one



Step 1: 2-Benzyl-5-bromo-pyridine

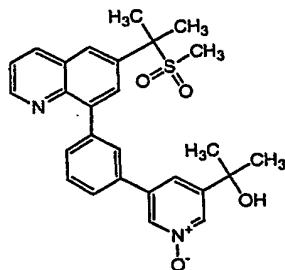
A mixture of 2,5-dibromopyridine (1.0eq.), benzyl alcohol (1.3eq.), KOH (2.4eq.) and DB-18-C-6 (0.05eq.) in toluene (0.3M) was refluxed for 3h, then 5 stirred overnight at rt. The mixture was concentrated, poured in water and extracted with Tol (2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated. Recrystallization in Hex:Et₂O afforded the title compound as a white solid.

Step 2: 8-[3-(6-Benzyl-2-methoxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-10 ethyl)-quinoline.

Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 2-benzyl-5-bromo-pyridine as starting material. Upon completion of the reaction (1h) the title compound was isolated by flash chromatography (Tol:Ace; 9:1) as a light yellow solid.

15 Step 3: EXAMPLE 19

To a solution of 8-[3-(6-Benzyl-2-methoxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 2 (1.0eq.) in CH₂Cl₂ (0.2M) 20 was added an equi volume of TFA. The mixture was stirred for 72h, concentrated, poured in saturated aqueous NaHCO₃ and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂:MeOH ; 95:5) afforded the title compound as a light yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.95 (dd, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.04 (d, 1H), 7.89 (dd, 1H), 7.79 (s, 1H), 7.75 (s, NH), 7.63-7.53 (m, 4H), 6.46 (d, 1H), 2.82 (s, 3H), 1.94 (s, 6H).

EXAMPLE 20**2-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-3-yl)-propan-2-ol****5 Step 1: 2-(5-Bromo-pyridin-3-yl)-propan-2-ol**

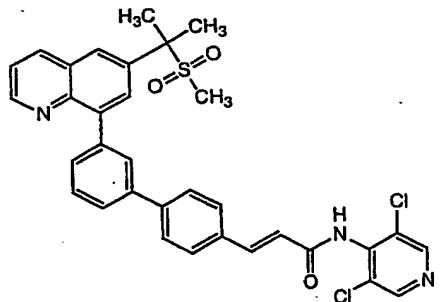
To a solution of 5-bromo-nicotinic acid ethyl ester (1.0eq.) in Et₂O (0.3M) at -30°C was added MeMgBr (2.7eq.; 3M in Et₂O). The mixture was refluxed for 2h, poured in 0.5M aqueous NaH₂PO₄ and extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:Et₂O:CH₂Cl₂; 2:1:2) afforded the title compound as a yellow oil.

Step 2: 2-(5-Bromo-1-oxy-pyridin-3-yl)-propan-2-ol

Prepared according to the procedure described in EXAMPLE 9, Step 4, but using 2-(5-bromo-pyridin-3-yl)-propan-2-ol as starting material. Flash chromatography (CH₂Cl₂:EtOH; 9:1) afforded the title compound as a white solid.

Step 3: EXAMPLE 20

Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 2-benzyloxy-5-bromo-pyridine as starting material. Upon completion of the reaction (1h) the title compound was isolated by flash chromatography (EtOAc:MeOH; 8.5:1.5) as a light yellow solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.32 (s, 1H), 8.28 (s, 1H), 8.26 (s, 1H), 8.20 (d, 1H), 8.03 (t, 1H), 7.74 (m, 2H), 7.67 (d, 1H), 7.54 (m, 2H), 5.05 (s, OH), 2.72 (s, 3H), 1.98 (s, 6H), 1.58 (s, 6H).

EXAMPLE 21**N-(3,5-Dichloro-pyridin-4-yl)-3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acrylamide**

- 5 **Step 1:** 3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-carbaldehyde

Prepared according to the procedure described in EXAMPLE 4 but using (4-formyl-phenyl)-boronic acid as starting material. Flash chromatography (Hex:EtOAc ; 1:1) afforded the title compound as a white solid.

- 10 **Step 2:** 3-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl}-acrylic acid.

Prepared according to the procedure described in EXAMPLE 11, Step 2, but using 3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-carbaldehyde from Step 1 as starting material. Stirring in Hex:Et₂O (8:2) afforded the title compound after filtration.

Step 3: 3-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl}-acrylic acid 4-nitro-phenyl ester

Prepared according to the procedure described in EXAMPLE 11, Step 3 but using 3-{3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl}-acrylic acid and 4-nitro-phenol as starting materials. Stirring in Et₂O afforded the title compound after filtration.

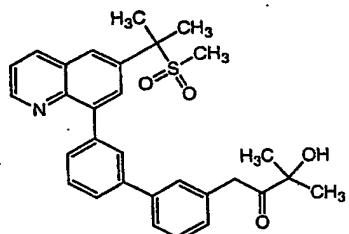
Step 4: EXAMPLE 21

To a solution of 3,5-dichloro-pyridin-4-ylamine (1.5eq.) in DMF (0.1M) was added *t*-BuONa (1.5eq.). The mixture was stirred for 15 min then 3-{3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl}-acrylic acid 4-nitro-phenyl ester (1.0eq.) was added. The final mixture was stirred for 12h, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic

extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (Hex:EtOAc; 9:1 to 1:9 in 20min) afforded the title compound as a yellow solid. ^1H NMR (400 MHz, acetone- d_6): δ 9.44 (br s, 1H), 8.97 (dd, 1H), 8.64 (s, 2H), 8.50 (dd, 1H), 8.33 (d, 1H), 8.26 (d, 1H), 8.11 (t, 1H), 7.87-7.77 (m, 7H), 5 7.65-7.60 (m, 2H), 7.09 (d, 1H), 2.81 (s, 3H), 2.04 (s, 6H).

EXAMPLE 22

3-Hydroxy-1-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-3-methyl-butan-2-one



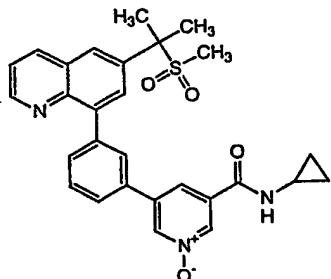
10

Step 1: 1-(3-Bromo-phenyl)-3-hydroxy-3-methyl-butan-2-one

A mixture of 1,3-dibromobenzene (1.0eq.), 3-hydroxy-3-methyl-butan-2-one (1.0eq.), $\text{Pd}_2(\text{dba})_3$ (0.02eq.), xantphos (0.04eq.) and *t*-BuONa (1.1eq.) in THF (0.15M) was stirred at 60°C for 2h, poured in saturated aqueous NH_4Cl and extracted (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (Hex:EtOAc; 7:3) afforded the title compound as an oil.

Step 2: EXAMPLE 22

Prepared according to the procedure described in EXAMPLE 6, Step 20 2, but using 1-(3-bromo-phenyl)-3-hydroxy-3-methyl-butan-2-one from Step 1 as starting material. Upon completion of the reaction (1h) the title compound was isolated by flash chromatography (EtOAc:MeOH ; 1:1 to 3:7) as a light yellow solid. ^1H NMR (500 MHz, acetone- d_6): δ 8.95 (d, 1H), 8.49 (d, 1H), 8.32 (d, 1H), 8.23 (d, 1H), 8.03 (s, 1H), 7.72 (t, 2H), 7.62-7.58 (m, 4H), 7.43 (t, 1H), 7.25 (d, 1H), 4.45 (s, 1H), 4.15 (s, 2H), 2.75 (s, 3H), 2.03 (s, 6H), 1.38 (s, 6H).

EXAMPLE 23**N-Cyclopropyl-5-[3-{6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl}-phenyl]-1-oxy-nicotinamide****5 Step 1: 5-Bromo-N-cyclopropyl-nicotinamide**

Prepared according to the procedure described in EXAMPLE 11 (Step 3) but using 5-bromo-nicotinic acid as starting material. Flash chromatography (EtOAc) afforded the title compound as a white solid.

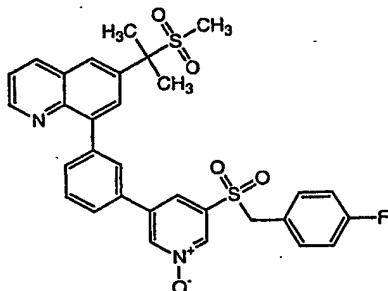
Step 2 : 5-Bromo-N-cyclopropyl-1-oxy-nicotinamide

10 Prepared according to the procedure described in EXAMPLE 9 (Step 4) but using 5-bromo-N-cyclopropyl-nicotinamide from Step 1 as starting material. Flash chromatography (EtOAc:MeOH ; 9:1) afforded the title compound as a white solid.

Step 3: EXAMPLE 23

15 Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 5-bromo-N-cyclopropyl-1-oxy-nicotinamide from Step 2 as starting material. Upon completion of the reaction (1h), flash chromatography (EtOAc:MeOH ; 4:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.94 (dd, 1H), 8.58 (s, 1H), 8.53 (s, 1H), 8.47 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 8.19 (s, NH), 8.09 (s, 1H), 8.00 (s, 1H), 7.78 (dd, 2H), 7.63 (t, 1H), 7.58 (dd, 1H), 2.94 (m, 1H), 2.76 (s, 3H), 2.02 (s, 6H), 0.75 (m, 2H), 0.65 (m, 2H).

EXAMPLE 24

8-{3-[5-(4-Fluoro-phenylmethanesulfonyl)-1-oxy-pyridin-3-yl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline5 **Step 1 : [5-(2-Trimethylsilyl-ethylsulfanyl)-pyridin-3-yl]-boronic acid**

To a suspension of 3,5-dibromopyridine (1.0eq.) in Et₂O (0.18M) at -65°C was added dropwise *n*-BuLi (1.15eq.). The mixture was stirred for 30min then 1-trimethylsilyl-2-(2-trimethylsilyl-ethyldisulfanyl)-ethane (1.15eq.) was added. The resulting light orange solution was stirred at -65°C for 20min. Subsequently, a 10 second portion of *n*-BuLi (1.15 eq.) was added. After stirring for 45min, tri-*iso*-propylboronate (1.15eq.) was added. The final mixture was warmed slowly and stirred for 12h at rt, quenched with aqueous HCl (1M) to pH = 5, stirred for 30min, extracted with Et₂O (2x). The combined organic extracts were poured in aqueous NaOH (1N). The aqueous phase was washed with Et₂O (2x), neutralized to pH = 5 using HCl (1N) and extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated to afford the title compound as a white solid.

Step 2: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilyl-ethylsulfanyl)-pyridin-3-yl]-phenyl}-quinoline

20 A mixture of **Quinoline 3** (1.0eq.), [5-(2-trimethylsilyl-ethylsulfanyl)-pyridin-3-yl]-boronic acid (1.2eq.), Na₂CO₃ (2.5eq.; 2M in H₂O) and PdCl₂(dpff)₂ (0.06 eq.) in DME (0.2 M) was stirred at 80°C for 2.5h. The mixture was cooled to room temperature, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 3:7) and stirring in Hex:Et₂O (1:1) afforded the title compound as a white solid after filtration.

Step 3: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline

Prepared according to the procedure described in EXAMPLE 7 (Step 3) but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilanyl-ethylsulfanyl)-pyridin-3-yl]-phenyl}-quinoline from Step 2 as starting material. Upon completion of the reaction (4h) and work-up, the title compound (white solid) was isolated and used without any purification.

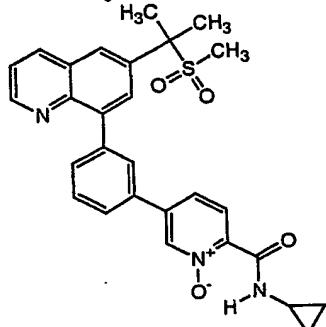
5 Step 4 : 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[1-oxy-5-(2-trimethylsilanyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline

Prepared according to the procedure described in EXAMPLE 9 (Step 4) but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilanyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline from step 3 as starting material. Flash chromatography (EtOAc:EtOH ; 95:5) and stirring in Et₂O afforded the title compound as a white solid after filtration.

10 Step 5: EXAMPLE 24

To a solution of 6-(1-methanesulfonyl-1-methyl-ethyl)-8-{3-[1-oxy-5-(2-trimethylsilanyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline from Step 4 (1.0eq.) in DMF (0.2M) was added tetramethyl-ammonium fluoride (2.4eq.). The mixture was stirred for 1h then 4-fluorobenzyl bromide (1.3eq.) was added. The final mixture was stirred for 1h, poured in water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (EtOAc:EtOH ; 95:5) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.97 (d, 1H), 8.73 (s, 1H), 8.51 (d, 2H), 8.35 (d, 1H), 8.30 (s, 1H), 8.25 (d, 1H), 8.07 (s, 1H), 7.88 (d, 1H), 7.76 (m, 1H), 7.69 (t, 1H), 7.63 (dd, 1H), 7.45-(dd, 2H), 7.12 (t, 2H), 4.84 (s, 2H), 2.76 (s, 3H), 2.03 (s, 6H).

EXAMPLE 25

5-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-oxy-pyridine-2-carboxylic acid cyclopropylamide5 **Step 1: 5-Bromo-pyridine-2-carboxylic acid cyclopropylamide**

To a solution of 5-bromo-pyridine-2-carboxylic acid methyl ester (1.0eq.) (*see Synth. Commun.*, 1997, 27, 515) in THF:MeOH (2:1; 0.2M) was added aqueous LiOH (1M; 3.0eq.). The mixture was stirred for 12h, concentrated and dried under vacuum. The residue was diluted in CH₂Cl₂ (0.2M), oxalyl chloride (8.0eq.) was added and the mixture was stirred for 3h, concentrated, dried under vacuum and diluted in CH₂Cl₂ (0.2M). Cyclopropylamine (10eq.) was added and the mixture was stirred for 2h, poured in saturated aqueous NaHCO₃ and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂:EtOAc; 9:1) afforded the title compound as a yellow solid.

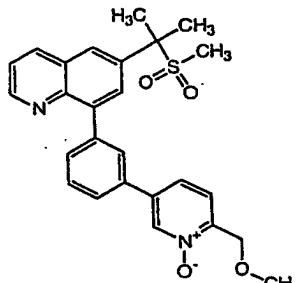
10 **Step 2: 5-Bromo-1-oxy-pyridine-2-carboxylic acid cyclopropylamide**

Prepared according to the procedure described in EXAMPLE 9 (Step 4) but using 5-bromo-pyridine-2-carboxylic acid cyclopropylamide from Step 1 as starting material. Flash chromatography (CH₂Cl₂:EtOAc; 9:1) afforded the title compound as a white solid.

15 **Step 3: EXAMPLE 25**

Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 5-bromo-1-oxy-pyridine-2-carboxylic acid cyclopropylamide from Step 2 as starting material. Flash chromatography (EtOAc) afforded the title compound as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 11.18 (d, NH), 8.94 (dd, 1H), 8.49 (d, 1H), 8.41 (d, 1H), 8.24 (d, 1H), 8.06 (s, 1H), 8.05 (s, 1H), 7.90 (s, 1H), 7.74 (d, 1H), 7.68 (dd, 1H), 7.60 (m, 2H), 7.45 (m, 1H), 2.96 (m, 1H), 2.61 (s, 3H), 1.97 (s, 6H), 0.83 (m, 2H), 0.64 (m, 2H).

EXAMPLE 26

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methoxymethyl-1-oxy-pyridin-3-yl)-phenyl]-quinoline

5

Step 1: 5-Bromo-pyridine-2-carbaldehyde

- To a solution of 2,5-dibromopyridine (1.0eq.) in Tol (0.1M) at -78°C was added *n*-BuLi (1.05eq.). The mixture was stirred for 2h at -78°C then DMF (3.0eq.) was added. The final mixture was stirred for 12h at -78°C, quenched using saturated aqueous NH₄Cl and extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 9:1) afforded the title compound as an oil.

Step 2: (5-Bromo-pyridin-2-yl)-methanol

- To a solution of 5-bromo-pyridine-2-carbaldehyde (1.0eq.) in THF:EtOH (1:1; 0.2M) at -78°C was added NaBH₄ (4.0eq.). The mixture was stirred for 2h at -78°C, quenched with excess AcOH, poured in aqueous HCl (1M), stirred for 15min, neutralized to pH = 7 with NaOH (1M) and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford the title compound as an oil.

Step 3: (5-Bromo-1-oxy-pyridin-2-yl)-methanol

- To a solution of (5-bromo-pyridin-2-yl)-methanol (1.0eq.) in CH₂Cl₂ (0.2M) was added peracetic acid (3.0eq.). The mixture was stirred for 12h, diluted with CH₂Cl₂ and neutralized with aqueous NaOH (1M) to pH = 7. The organic phase was decanted, dried over Na₂SO₄ and upon concentration the title compound crystallized as a white solid and was isolated by filtration.

Step 4: 5-Bromo-2-methoxymethyl-pyridine 1-oxide

- To a solution of (5-bromo-1-oxy-pyridin-2-yl)-methanol (1.0eq.) in THF:DMF (1:1; 0.2M) was added *t*-BuOK (1.0M in THF; 1.1eq.). The mixture was

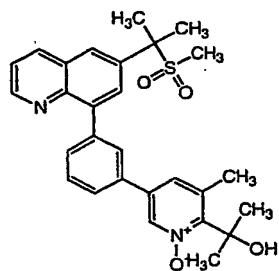
stirred for 1h, cooled to -78°C then MeI (1.1eq.) was added. The final mixture was warmed to rt, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to afford a mixture of the title compound and the starting material 5 (20%) which was used as such.

Step 5: EXAMPLE 26

A mixture of Quinoline 4 (1.2eq.), 5-bromo-2-methoxymethyl-pyridine 1-oxide (1.0eq.), PdCl₂(dpff)₂ (0.05eq.) and aqueous Na₂CO₃ (2M; 2.5eq.) in *n*-propanol (0.2M) was stirred at 80°C for 4h. The mixture was cooled, poured in 10 brine and extracted with EtOAc (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Flash chromatography (EtOAc:MeOH; 9:1) afforded the title compound as a light yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.95 (dd, 1H), 8.72 (s, 1H), 8.54 (dd, 1H), 8.30 (d, 1H), 8.08 (d, 1H), 7.98 (s, 1H), 7.79 (t, 1H), 7.77 (d, 1H), 7.75 (s, 1H), 7.66-7.62 (m, 2H), 7.56 (d, 1H), 4.62 (s, 2H), 15 3.48 (s, 3H), 2.51 (s, 3H), 1.95 (s, 6H).

EXAMPLE 27

2-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-methyl-1-oxy-pyridin-2-yl)-propan-2-ol



20

Step 1: 2,5-Dibromo-3-methyl-pyridine

5-Bromo-3-methyl-pyridin-2-ylamine (1.0eq.) was added portionwise to aqueous HBr (48%; 1.0M). The mixture was stirred 1h at rt then cooled to -20°C. Bromine (2.8eq.) was added dropwise followed by a aqueous solution of NaNO₂ 25 (1.0M; 2.7eq.). The final mixture was warmed to rt and stirred for 2h. The mixture was cooled back to -20°C then aqueous NaOH (1.0M; 3.0eq.) was added dropwise over 1h. The final mixture was warmed to rt and extracted with Et₂O (2x). The

combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated to afford the title compound as a yellow solid.

Step 2: 2-(5-Bromo-3-methyl-pyridin-2-yl)-propan-2-ol

- Prepared according to the procedure described in EXAMPLE 16 (Step 5) but using 2,5-dibromo-3-methyl-pyridine from Step 1 as starting material. Flash chromatography (Hex:EtOAc ; 9:1) afforded the title compound as a white solid.

Step 3: 2-(5-Bromo-3-methyl-1-oxy-pyridin-2-yl)-propan-2-ol

- Prepared according to the procedure described in EXAMPLE 9 (Step 10) but using 2-(5-bromo-3-methyl-pyridin-2-yl)-propan-2-ol from Step 2 as starting material. Flash chromatography (Hex:EtOAc ; 1:1) afforded the title compound as a white solid.

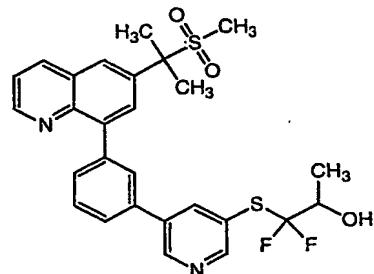
Step 4: EXAMPLE 27

- Prepared according to the procedure described in EXAMPLE 6 (Step 15) but using (5-bromo-3-methyl-1-oxy-pyridin-2-yl)-propan-2-ol from Step 3 as starting material. Flash chromatography (EtOAc) afforded the title compound as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 9.53 (s, OH), 9.00 (dd, 1H), 8.49 (d, 1H), 8.29 (dd, 1H), 8.10 (d, 2H), 7.90 (s, 1H), 7.78 (d, 1H), 7.64 (m, 2H), 7.52 (dd, 1H), 7.46 (d, 1H), 2.67 (s, 3H), 2.60 (s, 3H), 2.04 (s, 6H), 1.80 (s, 6H).

20

EXAMPLE 28

1,1-Difluoro-1-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-propan-2-ol



- Step 1: Difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid ethyl ester**
- Prepared according to the procedure described in EXAMPLE 24 (Step 5) but using 6-(1-methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilanyl-ethylsulfanyl)-pyridin-3-yl]-phenyl}-quinoline from EXAMPLE 24 (Step 2) and

bromo-difluoro-acetic acid ethyl ester as starting materials. Flash chromatography (Hex:EtOAc; 1:4) and stirring in Hex:Et₂O afforded the title compound as a white solid after filtration.

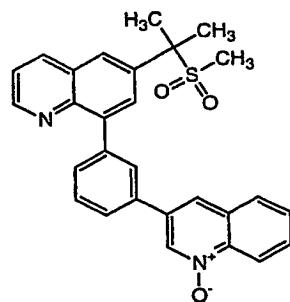
Step 2: EXAMPLE 28

5 To a solution of difluoro-(5-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-pyridin-3-ylsulfanyl)-acetic acid ethyl ester from Step 1 (1.0eq.) in CH₂Cl₂ (0.2M) at -78°C was added MeMgBr (3.0eq.; 3.0M in Et₂O). The mixture was warmed to rt, stirred for 12h, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in EtOH (0.2M) then NaBH₄ (3.0eq.) was added. The mixture was stirred for 2h, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 1:9) afforded the title compound as a white solid. ¹H NMR (400 MHz, acetone-*d*₆): δ 9.04 (d, 1H), 8.97 (dd, 1H), 8.75 (d, 1H), 8.50 (dd, 1H), 8.35-8.34 (m, 2H), 8.26 (d, 1H), 8.13 (s, 1H), 7.85 (dt, 1H), 7.82 (dt, 1H), 7.68 (t, 1H), 7.61 (dd, 1H), 5.15 (d, 1H), 4.20 (m, 1H), 2.76 (s, 3H), 2.03 (s, 6H), 1.37 (d, 3H).

20

EXAMPLE 29

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(1-oxy-quinolin-3-yl)-phenyl]-quinoline



Step 1: 3-Bromo-quinoline 1-oxide

25 To a solution of 3-bromo-quinoline (1.0eq.) in CH₂Cl₂ (0.2M) was added peracetic acid (2.0eq.). The mixture was stirred for 12h, poured in saturated aqueous NaHCO₃ and extracted with EtOAc (2x). The combined organic extracts

were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Crystallization from $\text{CH}_2\text{Cl}_2\text{:Hex}$ afforded the title compound as a white solid.

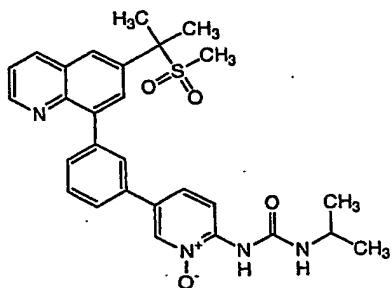
Step 2: EXAMPLE 29

- Prepared according to the procedure described in EXAMPLE 6 (Step 5) 2) but using 3-bromo-quinoline 1-oxide as starting material. Flash chromatography (EtOAc:MeOH ; 95:5) afforded the title compound as a white solid. ^1H NMR (500 MHz, CDCl_3): δ 8.99 (d, 1H), 8.93 (s, 1H), 8.75 (d, 1H), 8.29 (dd, 1H), 8.12 (s, 2H), 8.03 (s, 1H), 7.99 (s, 1H), 7.92 (d, 1H), 7.75 (m, 3H), 7.67 (m, 2H), 7.51 (dd, 1H), 2.66 (s, 3H), 2.03 (s, 6H).

10

EXAMPLE 30

1-Isopropyl-3-(5-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-oxy-pyridin-2-yl)-urea



15 **Step 1: 1-(5-Bromo-pyridin-2-yl)-3-isopropyl-urea**

To a solution of 2-amino-5-bromo-pyridine (1.05eq.) in THF (0.2M) was added DBU (1.0eq.) followed by *iso*-propyl-isocyanate (1.0eq.). The mixture was stirred for 12h, diluted with CH_2Cl_2 , washed with brine, dried over MgSO_4 , filtered and concentrated. Crystallization from acetone afforded the title compound as a white solid.

20 **Step 2: 1-(5-Bromo-1-oxy-pyridin-2-yl)-3-isopropyl-urea**

Prepared according to the procedure described in EXAMPLE 29 (Step 1) but using 1-(5-bromo-pyridin-2-yl)-3-isopropyl-urea from Step 1 as starting material. Crystallization from acetone afforded the title compound as a white solid.

25 **Step 3: EXAMPLE 30**

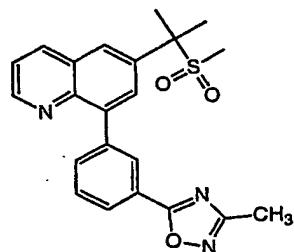
Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 1-(5-bromo-1-oxy-pyridin-2-yl)-3-isopropyl-urea from Step 2 as starting material. Flash chromatography (EtOAc:MeOH; 9:1) and stirring in acetone afforded

the title compound as a white solid after filtration. ^1H NMR (500 MHz, CDCl_3): δ 10.05 (s, NH), 8.98 (d, 1H), 8.59 (d, 1H), 8.41 (s, 1H), 8.29 (d, 1H), 8.09 (d, 2H), 7.88 (s, 1H), 7.70 (m, 3H), 7.55 (m, 3H), 3.96 (m, 1H), 2.65 (s, 3H), 2.01 (s, 6H), 1.20 (s, 6H).

5

EXAMPLE 31

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-quinoline



10 **Step 1:** 3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzoic acid methyl ester

To a solution of 3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzaldehyde (1.0eq.) (see WO-0146151) in $\text{CH}_2\text{Cl}_2:\text{MeOH}$ (1:1; 0.1M) was added NaCN (1.8eq.), MnO_2 (8.0eq.) and AcOH (0.05eq.). The mixture was stirred for 12h, filtered on celite, and concentrated. Flash chromatography (Hex:EtOAc; 1:1) afforded the title compound as a white solid.

15 **Step 2:** 3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzoic acid

To a solution of 3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzoic acid methyl ester from **Step 1** (1.0eq.) in THF (0.2M) was added aqueous LiOH (1.0M; 3.0eq.). The mixture was stirred for 5h at 60°C, neutralized to pH = 5 using aqueous HCl (1M) and extracted with CH_2Cl_2 (4x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. Stirring in Hex:Et₂O (1:1) afforded the title compound after filtration.

20 **Step 3: EXAMPLE 31**

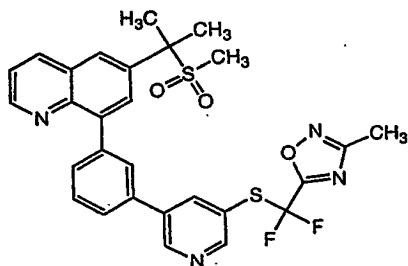
25 To a solution of -[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzoic acid from **Step 2** (1.0eq.) in DMF (0.1M) was added CDI (2.0eq.) and N-hydroxy-acetamidine (2.0eq.). The mixture was stirred for 1h at rt then 12h at 120°C. The mixture was cooled, poured in water and extracted with EtOAc. The organic extract was washed with water (2x), brine, dried over Na_2SO_4 , filtered and

concentrated. Flash chromatography (Hex:EtOAc; 9:1 to 1:9 in 20min) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.91 (dd, 1H), 8.52 (m, 3H), 8.38 (d, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.78 (t, 1H), 7.64 (dd, 1H), 2.77 (s, 3H), 2.43 (s, 3H), 2.05 (s, 6H).

5

EXAMPLE 32

8-(3-{5-[Difluoro-(3-methyl-[1,2,4]oxadiazol-5-yl)-methylsulfanyl]-pyridin-3-yl}-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



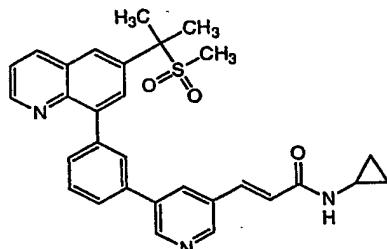
10 **Step 1:** Difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid

Prepared according to the procedure described in EXAMPLE 31 (Step 2) but using difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid ethyl ester from EXAMPLE 28 (Step 1) as 15 starting material.

Step 2: EXAMPLE 32

Prepared according to the procedure described in EXAMPLE 31 (Step 3) but using difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid from Step 1 as starting material. Flash 20 chromatography (Hex:AcOEt ; 1:4) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 9.07 (d, 1H), 8.97 (dd, 1H), 8.76 (d, 1H), 8.51 (dd, 1H), 8.37 (t, 1H), 8.35 (d, 1H), 8.26 (d, 1H), 8.17 (s, 1H), 7.85 (t, 2H), 7.70 (t, 1H), 7.62 (dd, 1H), 2.78 (s, 3H), 2.28 (s, 3H), 2.05 (s, 6H).

EXAMPLE 33

N-Cyclopropyl-3-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-yl)-acrylamide5 **Step 1: 5-Bromo-pyridine-3-carbaldehyde**

To a solution of 3,5-dibromopyridine (1.0eq.) in Et₂O (0.1M) at -78°C was added *n*-BuLi (1.05eq.). The mixture was stirred for 30min at -78°C then DMF (3.0eq.) was added. The final mixture was warmed to rt, stirred for 3h, quenched using saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 4:1) afforded the title compound as an oil.

10 **Step 2: 3-(5-Bromo-pyridin-3-yl)-acrylic acid**

Prepared according to the procedure described in Example 11 (Step 2) but using 5-bromo-pyridine-3-carbaldehyde from Step 1 as starting material.

15 **Step 3: 3-(5-Bromo-pyridin-3-yl)-N-cyclopropyl-acrylamide**

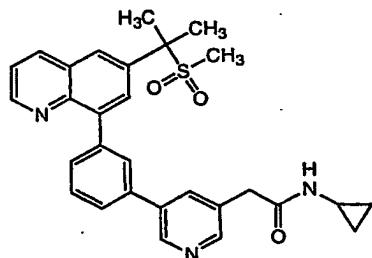
Prepared according to the procedure described in Example 11 (Step 3) but using 3-(5-bromo-pyridin-3-yl)-acrylic acid from Step 2 as starting material. Crystallization in CH₂Cl₂ afforded the title compound.

20 **Step 4: EXAMPLE 33**

Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 3-(5-bromo-pyridin-3-yl)-N-cyclopropyl-acrylamide from Step 3 as starting material. Flash chromatography (EtOAc:EtOH ; 9:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.98 (dd, 1H), 8.80 (d, 1H), 8.60 (d, 1H), 8.33 (dd, 1H), 8.07 (d, 2H), 8.01 (s, 1H), 7.89 (s, 1H), 7.73 (d, 1H), 7.60 (m, 3H), 7.45 (dd, 1H), 6.58 (d, 1H), 6.55 (s, NH), 2.80 (m, 1H), 2.65 (s, 3H), 1.98 (s, 6H), 0.75 (m, 2H), 0.55 (m, 2H).

EXAMPLE 34

N-Cyclopropyl-2-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-yl)-acetamide



5 **Step 1: 2-(5-Bromo-pyridin-3-yl)-N-cyclopropyl-acetamide**

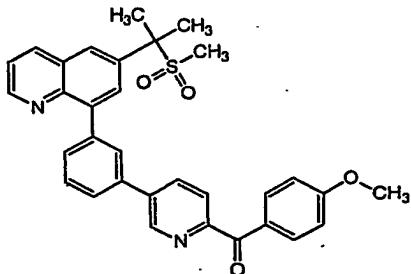
Prepared according to the procedure described in EXAMPLE 11 (Step 3) but using (5-bromo-pyridin-3-yl)-acetic acid as starting material. Crystallization in CH₂Cl₂ afforded the title compound.

Step 2: EXAMPLE 34

10 Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 2-(5-bromo-pyridin-3-yl)-N-cyclopropyl-acetamide from Step 1 as starting material. Flash chromatography (EtOAc:EtOH; 9:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.92 (dd, 1H), 8.79 (d, 1H), 8.47 (s, 1H), 8.45 (d, 1H), 8.30 (d, 1H), 8.21 (d, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.75 (d, 1H), 7.72 (d, 1H), 7.62 (t, 1H), 7.57 (dd, 1H), 7.41 (br s, NH), 3.54 (s, 2H), 2.72 (s, 3H), 2.68 (m, 1H), 2.00 (s, 6H), 0.61 (m, 2H), 0.40 (m, 2H).

EXAMPLE 35

20 **(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-2-yl)-(4-methoxy-phenyl)-methanone**



Step 1: (5-Bromo-pyridin-2-yl)-(4-methoxy-phenyl)-methanol

To a solution of 2,5-dibromopyridine (1.0eq.) in Tol (0.1M) at -78°C was added *n*-BuLi (1.05eq.). The mixture was stirred for 2h at -78°C then 4-methoxybenzaldehyde (1.1eq.) was added. The final mixture was warmed 0°C, poured in saturated aqueous NH₄Cl and extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 9:1 to 3:2) and stirring in Hex:Et₂O afforded the title compound as a white solid after filtration.

Step 2: (5-Bromo-pyridin-2-yl)-(4-methoxy-phenyl)-methanone

To a solution of (5-bromo-pyridin-2-yl)-(4-methoxy-phenyl)-methanol (1.0eq.) in EtOAc (0.2M) was added MnO₂ (3.0eq.). The mixture was stirred for 1h, filtered on celite and concentrated to afford the title compound as a white solid.

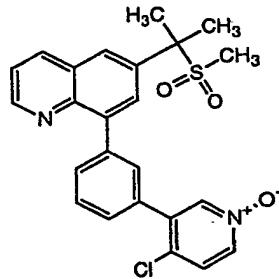
Step 3: EXAMPLE 35

Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using (5-bromo-pyridin-2-yl)-(4-methoxy-phenyl)-methanone from Step 2 as starting material. Flash chromatography (Hex:EtOAc; 9:1 to 1:4) afforded the title compound as a foam. ¹H NMR (500 MHz, acetone-*d*₆): δ 9.08 (d, 1H), 8.96 (dd, 1H), 8.48 (dd, 1H), 8.36 (dd, 1H), 8.32 (d, 1H), 8.26-8.19 (m, 4H), 8.09 (s, 1H), 7.86 (t, 2H), 7.68 (t, 1H), 7.60 (dd, 1H), 7.06 (d, 2H), 3.9 (s, 3H), 2.74 (s, 3H), 2.01 (s, 6H).

20

EXAMPLE 36

8-[3-(4-Chloro-1-oxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



25 **Step 1: 4-Chloro-3-tributylstannanyl-pyridine**

To a solution of LDA (1.2eq.) in THF (0.2M) at -78°C was added 4-chloro-pyridine (1.0eq.). The mixture was stirred for 1.5h at -78°C then Bu₃SnCl (1.5eq.) was added. The final mixture was slowly warmed to rt, poured in saturated

aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 95:5) afforded the title compound as an oil.

Step 2: 8-[3-(4-Chloro-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

5

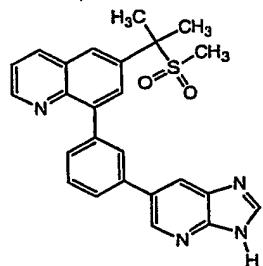
A mixture of Quinoline 3 (1.0eq.), 4-chloro-3-tributylstannanyl-pyridine (2.0eq.), PdCl₂(dppf)₂ (0.05eq.), CuI (0.05eq.) in dioxane (0.1M) was refluxed for 12h, cooled to rt and concentrated. Flash chromatography (CH₂Cl₂:MeOH ; 99:1) afforded the title compound as a beige foam.

10 **Step 3: EXAMPLE 36**

Prepared according to the procedure described in EXAMPLE 9 (Step 4) but using 8-[3-(4-chloro-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 2 as starting material. Flash chromatography (CH₂Cl₂:MeOH ; 95:5) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.96 (dd, 1H), 8.49 (d, 1H), 8.33 (dd, 2H), 8.26 (d, 1H), 8.19 (dd, 1H), 7.96 (s, 1H), 7.93 (d, 1H), 7.67 (t, 1H), 7.62 (m, 1H), 2.76 (s, 3H), 2.05 (s, 6H).

EXAMPLE 37

20 **8-[3-(3*H*-Imidazo[4,5-*b*]pyridin-6-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**



Step 1: 6-Bromo-3-(2-trimethylsilanyl-ethoxymethyl)-3*H*-imidazo[4,5-*b*]pyridine

To a solution of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine (1.0eq.) (see *J. Am. Chem. Soc.* 1957, 6421.) in DMF (0.2M) was added NaH (1.4eq.). The mixture

25 was stirred for 30min then SEM-Cl (2.0eq.) was added. The final mixture was stirred for 2h, poured in saturated aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with water (3x), brine, dried over Na₂SO₄,

filtered and concentrated. Flash chromatography (Hex:EtOAc; 7:3) afforded the title compound as a foam.

Step 2: 6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazo[4,5-*b*]pyridin-6-yl]-phenyl}-quinoline

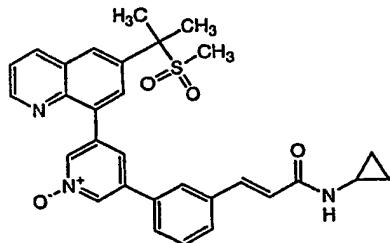
5 Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 6-bromo-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazo[4,5-*b*]pyridine from Step 1 as starting material. Flash chromatography (Hex:EtOAc ; 2:1 to 1:1) afforded the title compound as a foam.

Step 3: EXAMPLE 37

10 A mixture of 6-(1-methanesulfonyl-1-methyl-ethyl)-8-{3-[3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazo[4,5-*b*]pyridin-6-yl]-phenyl}-quinoline from Step 2 (1.0eq.), TBAF (2.0eq.) and ethylene diamine (1.5eq.) in DMF (0.2M) was stirred at 80°C for 3h. The mixture was cooled, diluted with water, filtered. The resulting solid was stirred in acetone to afford the title compound after filtration. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.94 (dd, 1H), 8.72 (s, 1H), 8.52 (dd, 1H), 8.47 (s, 1H), 8.30-8.25 (m, 2H), 8.08 (d, 1H), 7.98 (s, 1H), 7.79 (d, 1H), 7.68 (d, 1H), 7.63-7.60 (m, 2H), 2.81 (s, 3H), 1.93 (s, 6H).

EXAMPLE 38

20 **N-Cyclopropyl-3-(3-{5-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-1-oxy-pyridin-3-yl}-phenyl)-acrylamide**



Step 1: 8-(5-Bromo-pyridin-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

To a solution of 3,5-dibromo-pyridine (1.2eq.) in Et₂O (0.1M) at -78°C 25 was added dropwise *sec*-BuLi (1.05eq.). The mixture was stirred for 30min then tri-isopropyl boronate (1.5eq.) was added. The final mixture was warm to rt, diluted with iso-propanol and concentrated. To the residue in *n*-propanol (0. 1M) was added Quinoline 3 (1.0eq.), Na₂CO₃ (2M in H₂O; 3.5eq.), Pd(OAc)₂ (0.05eq.) and PPh₃ (0.15eq). The mixture was stirred at 80°C for 2h, cooled to rt, poured in saturated

aqueous NH₄Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (CH₂Cl₂:EtOAc; 1:1 to 0:1) afforded the title compound as a white solid.

5 **Step 2 : 8-(5-Bromo-1-oxy-pyridin-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**

Prepared according to the procedure described in EXAMPLE 9 (Step 4) but using 8-(5-bromo-pyridin-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 1 as starting material. Flash chromatography (EtOAc:EtOH ; 10 4:1) afforded the title compound as a white solid.

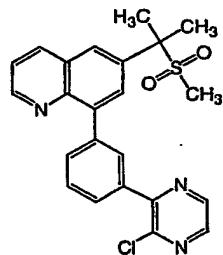
Step 3: 3-(3-{5-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-1-oxy-pyridin-3-yl}-phenyl)-acrylic acid

15 Prepared according to the procedure described in EXAMPLE 6 (Step 2) but using 3-(2-carboxy-vinyl)phenyl boronic acid and 8-(5-Bromo-1-oxy-pyridin-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 2 as starting materials. Flash chromatography (EtOAc:EtOH; 9:1) and stirring in CH₂Cl₂:Hex afforded the title compound as a white solid after filtration.

Step 4: EXAMPLE 38

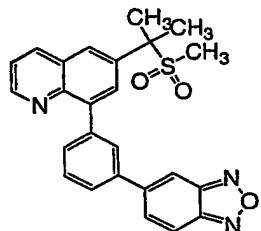
20 Prepared according to the procedure described in EXAMPLE 11 (Step 3) but using -(3-{5-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-1-oxy-pyridin-3-yl}-phenyl)-acrylic acid from Step 3 as starting material. Flash chromatography (EtOAc:EtOH ; 4:1) afforded the title compound as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 8.95 (dd, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 8.27 (d, 1H), 8.12 (m, 2H), 7.80 (s, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 7.50 (m, 4H), 6.48 (d, 1H), 6.20 (br s, NH), 2.86 (m, 1H), 2.70 (s, 3H), 2.03 (s, 6H), 0.82 (m, 2H), 0.57 (m, 2H).

EXAMPLE 39

8-[3-(3-Chloro-pyrazin-2-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

5 A mixture of Quinoline 4 (1.0eq.), 2,3-dichloro-pyrazine (3.0eq.),
 Pd(IMes)₂ (0.05eq.) and Na₂CO₃ (2M, 3.5eq.) in 1,4-dioxane (0.2M) was stirred at
 100°C for 2h. The mixture was cooled to rt, poured in saturated aqueous NH₄Cl and
 extracted with EtOAc (2x). The combined organic extracts were washed with brine,
 dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc;
 10 7:3) afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ
 8.94 (dd, 1H), 8.72 (d, 1H), 8.47 (m, 1H), 8.46 (dd, 1H), 8.32 (d, 1H), 8.25 (m, 2H),
 7.92 (d, 1H), 7.89 (d, 1H), 7.66 (t, 1H), 7.57 (dd, 1H), 2.74 (s, 3H), 2.02 (s, 6H).

EXAMPLE 40

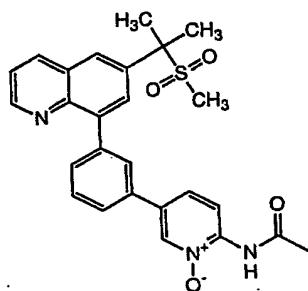
15 8-(3-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

Prepared according to the procedure described in EXAMPLE 3, but
 using 5-Bromo-benzo[1,2,5]oxadiazole (*Biorg. Med. Chem. Lett.* 2002, 233) as
 20 starting material. The reaction mixture was stirred 12h at 80°C. Flash
 chromatography (Hex:EtOAc 5 to 50% in 20min) and crystallization in Hex:EtOAc
 afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ
 8.98 (dd, 1H), 8.52 (dd, 1H), 8.35 (d, 1H), 8.28 (d, 1H), 8.26 (t, 1H), 8.23 (t, 1H),

8.11 (dd, 1H), 8.08 (dd, 1H), 7.93 (dd, 1H), 7.89 (dd, 1H), 7.71 (t, 1H), 7.63 (dd, 1H),
2.76 (s, 3H), 2.04 (s, 6H).

EXAMPLE 41

- 5 N-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-acetamide



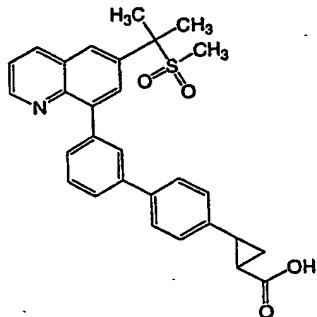
Step 1 : N-(5-Bromo-pyridin-2-yl)-acetamide

- To a solution of 5-bromo-pyridin-2-ylamine (1.0eq.), NEt_3 (1.2eq.) in CH_2Cl_2 (0.1M) was added AcCl (1.2eq.). The mixture was stirred 1h at rt, poured in saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography ($\text{CH}_2\text{Cl}_2:\text{EtOAc}$; 85:15) afforded the title compound as a white solid.
- Step 2: N-(5-Bromo-1-oxy-pyridin-2-yl)-acetamide**

- 15 Prepared according to the procedure described in EXAMPLE 9, Step 4, but using N-(5-bromo-pyridin-2-yl)-acetamide from Step 1 as starting material. Flash chromatography (EtOAc) afforded the title compound as a white solid.

Step 3: EXAMPLE 41

- Prepared according to the procedure described in EXAMPLE 6, Step 2, but using N-(5-bromo-1-oxy-pyridin-2-yl)-acetamide from Step 2 as starting material. The reaction mixture was stirred 1.5h at 90 °C. Flash chromatography (EtOAc:EtOH; 85:15) afforded the title compound as a white solid. ^1H NMR (500 MHz, acetone- d_6): δ 10.15 (s, NH), 8.94 (dd, 1H), 8.60 (d, 1H), 8.49-8.43 (m, 2H), 8.32 (d, 1H), 8.21 (d, 1H), 8.06 (s, 1H), 7.80-7.73 (m, 3H), 7.65-7.57 (m, 2H), 2.72 (s, 3H), 2.36 (s, 3H), 2.01 (s, 6H).

EXAMPLE 42**2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid****5 Step 1: Trans-2-(4-Bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester**

To a solution of E-3-(4-bromo-phenyl)-acrylic acid ethyl ester and Pd(OAc)₂ (0.05eq.) in THF (0.2M) was added portionwise CH₂N₂ until the reaction was completed. NMR of aliquots monitored the reaction. The resulting mixture was concentrated and filtered on celite to afford the title compound as an oil.

10 Step 2: Trans-2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid ethyl ester

Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 2-(4-bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester from Step 2 as starting material. The reaction mixture was stirred 2h at 100°C. Flash chromatography (Hex:EtOAc 3:2) afforded the title compound as a foam.

15 Step 3: EXAMPLE 42

To a solution of 2-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid ethyl ester (1.0eq.) from Step 1, in THF:MeOH (2:1; 0.2M) was added aqueous LiOH (2M; .2.0eq.). The mixture was stirred for 12h at rt, quenched with HCl 10% and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated. Crystallization in Hex:EtOAc afforded the title compound as a white solid. ¹H NMR (400 MHz, acetone-*d*₆): δ 8.96 (dd, 1H), 8.50 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 8.03 (t, 1H), 7.73-7.68 (m, 4H), 7.63-7.59 (m, 2H), 7.32 (d, 2H), 2.75 (s, 3H), 2.53 (m, 1H), 2.03 (s, 6H), 1.97 (m, 1H), 1.56 (m, 1H), 1.46 (m, 1H).

The enantiomers of EXAMPLE 42 were isolated separately by the following procedure.

Step 4: E-3-(4-Bromo-phenyl)-1-imidazol-1-yl-propenone

To a solution of E-3-(4-Bromo-phenyl)-acrylic acid (1.0eq.) in toluene (0.2M) was added CDI (1.5eq.). The mixture was stirred for 3h at rt. The resulting precipitate was isolated by filtration to afford the title compound as a white solid.

Step 5: E-3-[3-(4-Bromo-phenyl)-acryloyl]-4-methyl-5-phenyl-oxazolidin-2-one

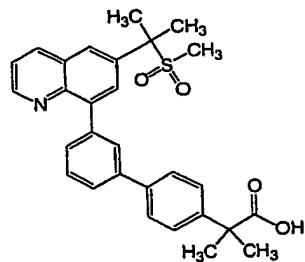
A mixture of 3-(4-Bromo-phenyl)-1-imidazol-1-yl-propenone (1.05eq.) from Step 4, (4R,5S)-(+) -4-methyl-5-phenyl-2-oxazolidinone (1.0eq.) and Et₃N (1.2 eq) in CH₃CN (0.2M) was reflux overnight. The resulting mixture was cooled to rt, filtered on a pad of silica gel and concentrated. Crystallization in Hex:Et₂O afforded the title compound as a white solid.

Step 6: Trans-3-[2-(4-Bromo-phenyl)-cyclopropanecarbonyl]-4-methyl-5-phenyl-oxazolidin-2-one

To a solution of E-3-[3-(4-Bromo-phenyl)-acryloyl]-4-methyl-5-phenyl-oxazolidin-2-one from Step 5 and Pd(OAc)₂ (0.05eq.) in THF (0.2M) was added portionwise CH₂N₂ until the reaction was completed. NMR of aliquots monitored the reaction. The resulting mixture was concentrated and flash chromatography (Hex:EtOAc ; 3:2) to afford the two separate diastereoisomers. Each diastereoisomers were submitted to the procedures described in Step 2 and Step 3 to afford the (+) and (-) enantiomers of EXAMPLE 42

EXAMPLE 43

2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2-methyl-propionic acid



Step 1: 2-(4-Bromo-phenyl)-2-methyl-propionic acid methyl ester

To a solution of (4-Bromo-phenyl)-acetic acid methyl ester (1.0eq) in DMF (0.2M) was added MeI (20eq) followed by NaH (2.2eq.) portion wise. The

mixture was stirred for 2h. An extra amount of NaH (1.1eq) was added. The final mixture was stirred for 12h, poured in saturated aqueous NH₄Cl and extracted with Et₂O (2x). The combined organic extracts were washed with water (3x), brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 95:5) 5 afforded the title compound as a foam.

Step 2 : 3-[3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl]-3-methyl-butric acid methyl ester

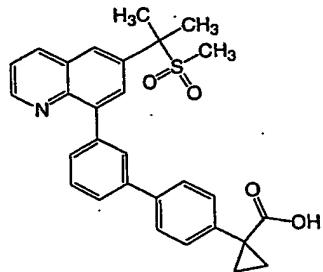
Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 2-(4-bromo-phenyl)-2-methyl-propionic acid methyl ester from Step 1 as 10 starting material. The reaction mixture was stirred 2h at 70°C. Flash chromatography (Hex:EtOAc; 3:2) afforded the title compound as a foam.

Step 3: EXAMPLE 43

To a solution of 3-[3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl]-3-methyl-butric acid methyl ester (1.0eq.) from Step 1, in 15 THF:MeOH (2:1; 0.2M) was added aqueous LiOH (2M; 5.0eq.). The mixture was stirred for 4h at 60°C, quenched with AcOH (20eq.), poured in brine and extracted with EtOAc (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. Crystallization in Hex:Et₂O:EtOAc afforded the title compound as 20 a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.93 (dd, 1H), 8.46 (dd, 1H), 8.29 (d, 1H), 8.21 (d, 1H), 8.02 (t, 1H), 7.72-7.68 (m, 4H), 7.59-7.51 (m, 4H), 2.72 (s, 3H), 2.00 (s, 6H), 1.59 (s, 6H).

EXAMPLE 44

1-[3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl]-cyclopropanecarboxylic acid



Step 1: 1-(4-Bromo-phenyl)-cyclopropanecarbonitrile (See *Org Prep. and Proc.*, 1995, 27, 355.)

A mixture of (4-bromo-phenyl)-acetonitrile (1.0eq.), 1-bromo-2-chloro-ethane (1.6eq.), triethylbenzyl ammonium chloride (0.03eq.) and aqueous NaOH 50% (6eq.) was stirred for 12h at 60°C. The resulting mixture was poured in water and extracted with Et₂O (2x). The combined organic extracts were washed with 5 HCl 5%, brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc; 95:5) afforded the title compound as a foam.

Step 2: 1-(4-Bromo-phenyl)-cyclopropanecarboxylic acid methyl ester

To a solution of -(4-bromo-phenyl)-cyclopropanecarbonitrile from Step 1 in EtOH (0.2M) was added NaOH 25% (10eq.). The mixture was stirred for 10 6h at 100°C, quenched with AcOH (20eq.), poured in brine, extracted with EtOAc (2x). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was dissolved in CH₂Cl₂ and diazomethane was added portionwise until the esterification was completed by TLC. Flash chromatography (Hex:EtOAc; 9:1) afforded the title compound as a colorless oil.

15 **Step 3: 1-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester.**

Prepared according to the procedure described in EXAMPLE 6, Step 2, but 1-(4-bromo-phenyl)-cyclopropanecarboxylic acid methyl ester from Step 2 as starting material. The reaction mixture was stirred 2 h at 70°C. Flash chromatography (Hex:EtOAc; 2:1) afforded the title compound as a foam.

Step 4: EXAMPLE 44

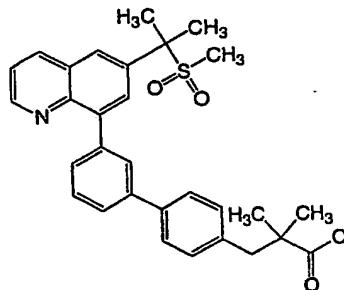
Prepared according to the procedure described in EXAMPLE 43, Step 3, but using 1-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester from Step 3 as starting material.

25 Crystallization in Hex:Et₂O afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.96 (dd, 1H), 8.50 (dd, 1H), 8.32 (d, 1H), 8.24 (d, 1H), 8.04 (t, 1H), 7.75-7.72 (m, 2H), 7.69 (d, 2H), 7.62-7.58 (m, 2H), 7.51 (d, 2H), 2.75 (s, 3H), 2.03 (s, 6H), 1.59 (dd, 2H), 1.26 (dd, 2H).

30

EXAMPLE 45

3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2,2-dimethyl-propionic acid



Step 1: 3-(4-Bromo-phenyl)-propionic acid tert-butyl ester

To a solution of cyclohexyl-isopropyl-amine (1.0eq.) in THF (2.0M) at -78°C was added dropwise *n*-BuLi (0.95eq.). The mixture was stirred at -78°C for 20min then a solution of acetic acid tert-butyl ester (1.0eq.) in THF (5.0M) was added dropwise. The resulting mixture was stirred at -78°C for 1h. A solution of 4-bromobenzyl bromide (0.9eq.) in THF (5.0M) was then added dropwise and the final mixture was warm slowly to rt and stirred for 12h. The reaction was quenched with cold aqueous HCl (1M), diluted water and extracted with Et₂O (2x). The combined organic extracts were washed with HCl (1M), brine, dried over Na₂SO₄, filtered and concentrated. The residue was distilled under vacuum (95°C, 0.4mmHg) to afford the title compound as a colorless oil.

Step 2: 3-(4-Bromo-phenyl)-2,2-dimethyl-propionic acid tert-butyl ester

To a solution of cyclohexyl-isopropyl-amine (1.2eq.) in THF (1.0M) at -78°C was added dropwise *n*-BuLi (1.2eq.). The mixture was stirred at -78°C for 20min then a solution of 3-(4-bromo-phenyl)-propionic acid tert-butyl ester from Step 1 (1.0eq.) in THF (5.0M) was added dropwise. The resulting mixture was stirred at -78°C for 30min then MeI (5.0eq.) was added. The final mixture was warm slowly to rt and stirred for 1h. The reaction was poured in cold aqueous HCl (0.5M) and extracted with Et₂O (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was resubmitted thrice to the above procedure until no mono-methyl compound was observed by NMR. Flash chromatography (Hex:EtOAc; 95:5) afforded the title compound as a colorless oil.

Step 3: 3-[3'-{6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2,2-dimethyl-propionic acid tert-butyl ester

Prepared according to the procedure described in EXAMPLE 6, step 2, but 3-(4-Bromo-phenyl)-2,2-dimethyl-propionic acid tert-butyl ester from Step 2 as

starting material. The reaction mixture was stirred 2h at 70°C. Flash chromatography (Hex:EtOAc 30 to 90% in 20min) afforded the title compound as a foam.

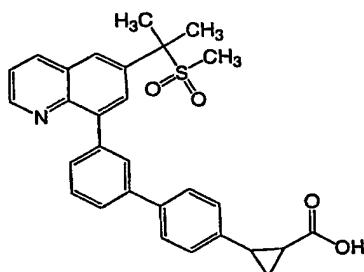
Step 4: EXAMPLE 45

- A solution of 3-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2,2-dimethyl-propionic acid tert-butyl ester from Step 3 in CH₂Cl₂:TFA (2:1) was stirred at rt for 12h. The resulting mixture was concentrated and diluted with water. The pH was adjusted to 5 using first NaOH (1M) then excess AcOH. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated.
- Crystallization in Hex:CH₂Cl₂ afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.93 (dd, 1H), 8.46 (dd, 1H), 8.29 (d, 1H), 8.21 (d, 1H), 8.00 (t, 1H), 7.71-7.68 (m, 2H), 7.63 (d, 2H), 7.59-7.54 (m, 2H), 7.32 (d, 2H), 2.93 (s, 2H), 2.72 (s, 3H), 2.00 (s, 6H), 1.19 (s, 6H).

15

EXAMPLE 46

2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid



Step 1: Z-3-(4-Bromo-phenyl)-acrylic acid methyl ester (*Tet Lett.* 1983, 4405)

- To a solution of [Bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-acetic acid methyl ester (1.0eq.) and 18-C-6 (5.0eq.) in THF (0.05M) at -78°C was added dropwise KN(TMS)₂ (1.0eq.). The mixture was stirred at -78°C for 15min then 4-bromobenzaldehyde (1.0eq.) was added. The final mixture stirred for 1h at -78°C, poured in saturated aqueous NH₄Cl and extracted with Et₂O (3x). The combined organic extracts were washed with, brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (Hex:EtOAc 10 to 25%) afforded a mixture of desired material and the starting aldehyde. Upon treatment in CH₂Cl₂ of the mixture

with Amino-Merrifield resin for 10min, the aldehyde was removed. Filtration and concentration afforded the title compound as an oil.

Step 2: Cis-2-(4-Bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester

Prepared according to the procedure described in **Example 42, Step 1,** 5 but using Z-3-(4-Bromo-phenyl)-acrylic acid methyl ester from **Step 1** as starting material Flash chromatography (Hex:EtOAc 85:15) afforded the title compound as a oil.

Step 3: Cis 2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester

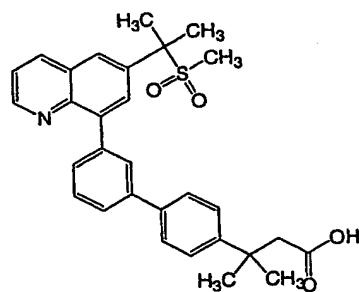
10 Prepared according to the procedure described in **EXAMPLE 6, Step 2,** but using 2-(4-bromo-phenyl)-cyclopropanecarboxylic acid ethyl ester from **Step 2** and PdCl₂(dpff)₂ as starting materials. The reaction mixture was stirred 2h at 60°C. Flash chromatography (Hex:EtOAc 35 to 50%) afforded the title compound as a foam.

15 Step 4: EXAMPLE 46

Prepared according to the procedure described in **EXAMPLE 42, Step 3,** but using Cis 2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester from **Step 3** as starting materials. Crystallization in Et₂O afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-*d*₆): δ 8.95 (dd, 1H), 8.49 (dd, 1H), 8.32 (d, 1H), 8.23 (d, 1H), 8.02 (t, 1H), 7.73-7.69 (m, 2H), 7.64-7.57 (m, 4H), 7.41 (d, 2H), 2.75 (s, 3H), 2.71-2.67 (m, 1H), 2.20-2.11 (m, 1H), 2.03 (s, 6H), 1.69-1.65 (m, 1H), 1.43-1.39 (m, 1H).

EXAMPLE 47

25 3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-3-methyl-butyric acid



Step 1: 3-(4-Iodo-phenyl)-3-methyl-butyric acid methyl ester

The corresponding acid was prepared according to the procedure described in *J. Am. Chem. Soc.* 1948, 70, 370 and was converted to the title compound using diazomethane in CH₂Cl₂.

Step 2: 3-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl]-3-methyl-butyric acid methyl ester

Prepared according to the procedure described in EXAMPLE 6, Step 2, but using 3-(4-Iodo-phenyl)-3-methyl-butyric acid methyl ester from Step 1 as starting material. The reaction mixture was stirred 2.5h at 70°C. Flash chromatography (Hex:EtOAc 1:1) afforded the title compound as a foam.

10 Step 3: EXAMPLE 47

Prepared according to the procedure described in EXAMPLE 43, Step 3, but using 3-[3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl]-3-methyl-butyric acid methyl ester from Step 2 as starting material. Crystallization in Hex:EtOAc afforded the title compound as a white solid. ¹H NMR (500 MHz, acetone-d₆): δ 8.93 (dd, 1H), 8.46 (dd, 1H), 8.29 (d, 1H), 8.22 (d, 1H), 8.02 (t, 1H), 7.74-7.65 (m, 4H), 7.61-7.53 (m, 4H), 2.73 (s, 3H), 2.70 (s, 2H), 2.01 (s, 6H), 1.49 (s, 6H).

The following compounds were prepared according to the procedure described previously. Indicated is their respective (M + 1)⁺ value obtained from a low resolution mass spectrometer under electron-spray ionization conditions.

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
48	6-Isopropyl-8-(4'-methanesulfonyl-biphenyl-3-yl)-quinoline	402.4
49	1-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-yl]-ethanone	444.3
50	1-[3-Hydroxy-3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-4-yl]-ethanone	460.3
51	1-[4-Hydroxy-3'-(6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-3-yl]-ethanone	460.3

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
52	8-(3'-Methanesulfonyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	480.2
53	8-(4'-Methanesulfonyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	480.2
54	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(5-trifluoromethyl-pyridin-2-yl)-phenyl]-quinoline	471.3
55	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(3-methyl-pyridin-2-yl)-phenyl]-quinoline	417.3
56	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-thiophen-2-yl-phenyl)-quinoline	408.3
57	1-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-thiophen-2-yl)-ethanone	450.4
58	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(3-methyl-thiophen-2-yl)-phenyl]-quinoline	422.3
59	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-thiophene-2-sulfonic acid amide	487.3
60	3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-carbonitrile	427.3
61	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-quinolin-3-yl-phenyl)-quinoline	453.3
62	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-3-yl-phenyl)-quinoline	403.3
63	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3-pyridin-4-yl-phenyl)-quinoline	403.3
64	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(3'-nitro-biphenyl-3-yl)-quinoline	447.2
65	8-(3-Benzo[1,3]dioxol-5-yl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	446.3
66	{4-Chloro-3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-methanol	466.4
67	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(5-methanesulfonyl-pyridin-3-yl)-phenyl]-quinoline	481.3

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
68	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-2-yl)-phenyl]-quinoline	449.3
69	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methylsulfanyl-pyridin-3-yl)-phenyl]-quinoline	449.3
70	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-acrylic acid methyl ester	486.3
71	3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-carbaldehyde	-
72	2,2,2-Trifluoro-1-{3'-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-ethanol	500.3
73	{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-methanol	432.2
74	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-acrylic acid methyl ester	486.4
75	8-(2'-Methanesulfonylmethyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	494.3
76	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[2'-([1,3,4]thiadiazol-2-ylsulfanyl methyl)-biphenyl-3-yl]-quinoline	532.3
77	{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-methanol	432.2
78	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acrylic acid methyl ester	-
79	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[2'-(1-methyl-1H-imidazol-2-ylsulfanyl methyl)-biphenyl-3-yl]-quinoline	528.3
80	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-propionic acid methyl ester	488.4
81	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-prop-2-en-1-ol	458.4
82	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-propan-1-ol	460.3

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
83	{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-methanol	432.2
84	2-(6-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-yl)-propan-2-ol	461.5
85	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-2-yl}-propionic acid	474.4
86	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methyl-pyridin-3-yl)-phenyl]-quinoline	337.1
87	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-acrylic acid	472.4
88	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-nicotinic acid ethyl ester	475.3
89	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[6-(propane-2-sulfonyl)-pyridin-3-yl]-phenyl}-quinoline	509.4
90	8-[3-(6-Benzyloxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	509.3
91	2-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-yl)-propan-2-ol	461.3
92	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-propionic acid	474.4
93	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilyl-ethylsulfanyl)-pyridin-3-yl]-phenyl}-quinoline	535.4
94	8-{3-[5-(4-Fluoro-benzylsulfanyl)-pyridin-3-yl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	543.2
95	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acrylic acid	472.4
96	N-Cyclopropyl-5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-nicotinamide	486.2
97	3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-5-trifluoromethyl-pyridin-2-ylamine	486.3

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
98	Dicyclopropyl-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-methanol	529.5
99	8-[3-(6-Ethanesulfonyl-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	495.3
100	2-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl})-pyridin-2-yl)-propan-2-ol	461.5
101	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[1-oxy-5-(2-trimethylsilanyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline	583.4
102	8-(3-{5-[1,2-Bis-(4-fluoro-phenyl)-ethanesulfonyl]-1-oxy-pyridin-3-yl}-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	699.3
103	8-[3-(5-Ethanesulfinyl-1-oxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	495.1
104	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(1-oxy-5-trifluoromethyl-pyridin-3-yl)-phenyl]-quinoline	487.3
105	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-[3-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-phenyl]-quinoline	495.9
106	3-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-pentan-3-ol	506.5
107	(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-3-yl)-methanol	449.3
108	Difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid ethyl ester	557.2
109	Difluoro-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-3-ylsulfanyl)-acetic acid	529.4
110	(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-methanol	449.3
111	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(5-phenyl-pyridin-3-yl)-quinoline	404.3

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
112	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(1-oxy-5-phenyl-pyridin-3-yl)-quinoline	420.0
113	1-Isopropyl-3-(5-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-pyridin-2-yl)-urea	502.6
114	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[5-(2-trimethylsilanyl-ethanesulfonyl)-pyridin-3-yl]-phenyl}-quinoline	567.4
115	8-[3-(4-Chloro-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	437.3
116	(5-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-pyridin-2-yl)-(4-methylsulfanyl-phenyl)-methanone	553.5
117	5-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-oxy-pyridine-2-carboxylic acid isopropylamide	504.4
118	3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl)-biphenyl-2-carbonitrile	427.3
119	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-(2'-methylsulfanyl-biphenyl-3-yl)-quinoline	448.2
120	8-(2'-Methanesulfonyl-biphenyl-3-yl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	480.2
121	1,1,1,3,3,3-Hexafluoro-2-(5-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-pyridin-3-yl)-propan-2-ol	569.7
122	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[6-(4-methoxy-benzyloxy)-pyridin-2-yl]-phenyl}-quinoline	539.4
123	6-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1H-pyridin-2-one	419.3
124	1,1,1,3,3,3-Hexafluoro-2-(5-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-oxy-pyridin-3-yl)-propan-2-ol	585.5
125	5-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-nicotinic acid	447.2

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
126	1,1,1,3,3-Hexafluoro-2-(5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridin-2-yl)-propan-2-ol	585.5
127	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridine-2-carboxylic acid methyl ester	477.2
128	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-pyridine-2-carboxylic acid	463.2
129	{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-acetic acid	460.3
130	3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-carboxylic acid	446.3
131	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-nicotinic acid	463.2
132	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-propionic acid methyl ester	488.4
133	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-propionic acid	474.4
134	2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid methyl ester	514.4
135	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-nicotinonitrile	444.3
136	3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-carboxylic acid amide	445.2
137	2-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-cyclopropanecarboxylic acid	486.4
138	5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-oxy-nicotinic acid 2,2-dimethyl-propionyloxymethyl ester	577.4
139	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2-methyl-propionic acid tert-butyl ester	544.4

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
140	3-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2-methyl-propionic acid	488.4
141	2-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-2-methyl-propionic acid methyl ester	502.2
142	{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acetic acid	460.3
143	1-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-cyclopropanecarboxylic acid amide	485.3
144	2-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-3-yl}-2-methyl-propionic acid	488.4
145	8-[3-(5-Chloro-1-oxy-pyridin-3-yl)-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline	453.3
146	(1-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-ylmethylsulfanylmethyl}-cyclopropyl)-acetic acid	560.3
147	(1-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-ylmethanesulfonyl-methyl}-cyclopropyl)-acetic acid	592.3
148	3-[3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acrylic acid methyl ester	486.4
149	1-{3'-(6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-ylmethyl}-cyclobutanecarboxylic acid	514.4
150	[1-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridin-2-ylsulfanylmethyl}-cyclopropyl]-acetic acid	547.4
151	[1-(5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-pyridine-2-sulfonylmethyl}-cyclopropyl]-acetic acid	579.4

EX.	Chemical name	ESI-LRMS (M + 1) ⁺
152	6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{4'-[2-(1H-tetrazol-5-yl)-cyclopropyl]-biphenyl-3-yl}-quinoline	510.3
153	(1-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-ylsulfanylmethyl}-cyclopropyl)-acetic acid	546.2
154	(1-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-sulfanylmethyl}-cyclopropyl)-acetic acid	578.4
155	3-{3'-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-biphenyl-4-yl}-acrylic acid	472.4

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.